HANDBOOK OF DISEASES OF THE BLOOD

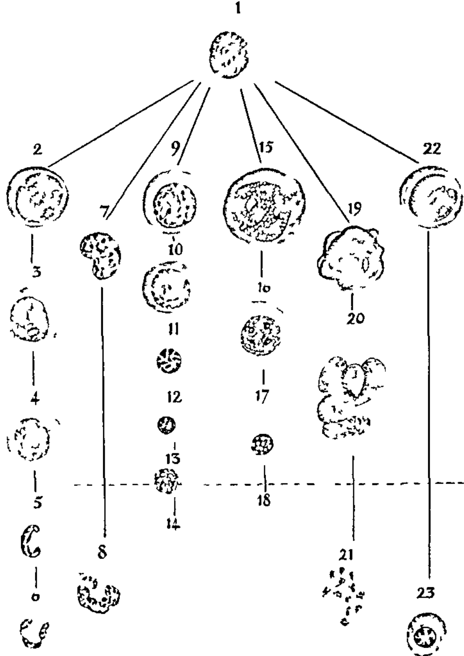
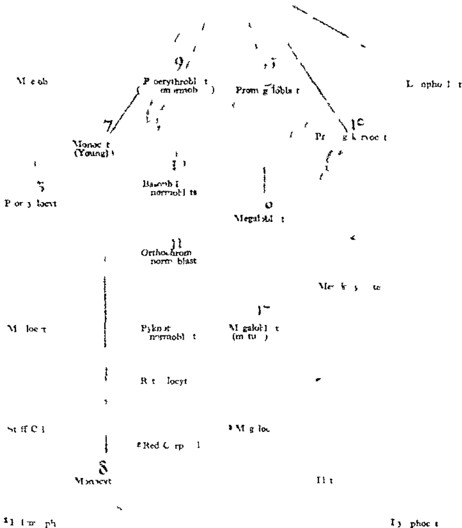


FIG 1 Genealogy of blood cells Cells b low the dotted lin are of the types normally found in the p ripheral blood


(Young)
Orthochrom

HANDBOOK OF DISEASES OF THE BLOOD

by

A PINEY, M D , M R C P

Physician Women s Hospital Plaistow late Director Pathological Department Cancer Hospital and Charing Cross Hospital Institute of Pathology London



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PREFACE

THE diseases of the blood and blood forming organs have most unfortunately tended more and more to become the province of the clinical pathologist to the exclusion of the physician That this is a lamentable state of affairs is obvious because it has arisen as a result of the feeling that bed-side observation of patients with blood dyscrasias gives less information—and that of less importance—than does laboratory investigation

It is of course obvious that the laboratory is essential for the diagnosis and control of treatment in many of these maladies but it is to me a fantastic idea that the physician who has after all the responsibility for the care of the patient should delegate so essential a procedure to the pathologist It is as if the cardiologist gave the task of interpreting the electrocardiograms of his patients to someone else Of course I am not suggesting that it is part of the duty of the cardiologist to be an expert in all the possible aspects of electro-physiology but he must be the master of the relevant diagnostic aids

The present book is an attempt to depict haematology as a primarily bedside subject which is the province of the physician who like his cardiological colleague must be able to deal with the fundamental laboratory work himself This is not an attempt to denigrate the clinical pathologist whose experience and skill are essential for the full investigation of cases needing specially complicated methods of laboratory examination All that is being asserted is that the physician haematologist must be competent to examine both the patient and the patient s haemopoietic system by all methods that are usually necessary

In the performance of this task the collaboration of the general physician and the general practitioner is essential and my hope is that I shall be able to present haematology in a manner useful to both The haematologist is more than adequately supplied with specialized books on his subject while the general physician has no suitable book he is therefore tempted to turn to his non-clinical colleagues for the information which he should be able to obtain for himself

The first step in the diagnosis of any of the haemic dyscrasias is a careful clinical examination it is most emphatically *not* the sending

of a specimen to the laboratory Indeed it is safe to assert that at least as many errors are made by laboratory examination as could possibly result from a purely clinical inquiry

With the aim of assisting the practitioner this book will have an unconventional arrangement, which will I hope make it useful to those for whom it is intended although admittedly it involves a certain amount of repetition Thus the main symptoms and signs will be described in some detail, before going on to a more systematic account of the various diseases and syndromes The most significant laboratory findings will be described in the appropriate places but without any attempt at a review of recent work that is not immediately applicable to diagnosis or treatment

It is my hope that this book may play some part in rescuing haematology from sepulture in the laboratory and in restoring it to its rightful place—the bed side

I am extremely grateful to Professor Benhamou of Algiers for permission to use his illustrations of the fundus oculi

A PINEY

SECTION I

SYMPTOMS AND SIGNS OF BLOOD DISEASES

INTRODUCTION

DISEASES of the blood and blood forming organs are not to be regarded as being essentially different in their nosological and aetiological relationships from other maladies affecting other systems Patients seek advice on account of some discomfort or disability that is to say their first appeal is to the clinician whose task it is to assess the significance of the symptoms and signs as fully as possible *before* calling on the aid of the laboratory True enough the laboratory has to play a very large part in the diagnosis of blood dyscrasias while it is often only by its findings that the success or otherwise of treatment can be determined Even so to divorce the laboratory findings from the clinical picture is dangerous and it is for this reason that the present section of this book has been divided into two parts the first essentially clinical deals with the manifestations of blood diseases in general the second which is mainly devoted to the results of laboratory investigation attempts to supply a broad outline of those haematological changes that are of direct clinical significance (what one might well regard as being of the nature of physical signs that can only be elicited in the laboratory)

Although much of the material in these two chapters will have to be repeated in subsequent ones it is essential that they should be read right through by anyone who is interested in *patients* suffering from blood diseases

It must also be remembered that hereditary factors play a part in the genesis of a considerable number of blood dyscrasias The mode of inheritance of haemophilia (p 173) is well known but it is less widely realized that some fortunately minor congenital abnormalities of the blood may be inherited in a cumulative manner For example the off spring of two persons who e blood shows the anomaly of elliptocytosis may present peculiar skeletal abnormalities associated with more or less severe anaemia

There is no logical order in clinical examination of patients but that employed here appears to be convenient

CHAPTER I

SYMPTOMS AND SIGNS OF BLOOD DISEASES (CLINICAL)

THE mode of approaching patients suspected of suffering from diseases of the blood follows the principles of clinical medicine in general but as in every specialty more stress has to be laid on some aspects than on others

The persistent or progressive *effects of past infection* and sometimes even if their *treatment* is perhaps more marked in connexion with haemic disorders than with most others so many factors influence the composition of the blood and its functional state that a very full history is essential For example treatment of painful diseases even in the past with more or less toxic *drugs* such as amidopyrine may explain the genesis of a case of agranulocytosis while the treatment of infections with drugs of the sulphonamide group may induce a similar state or even an acute haemolytic anaemia and indeed there are many other examples

Then again neither the patient s present occupation nor his past employment is necessarily irrelevant Some toxic substances employed in *industry* may manifest their ill effects rapidly in some people while others suffer no obvious damage until months or even years have passed since exposure to the substance has ceased One example will suffice here aplastic anaemia may develop in persons exposed to benzene at almost any time during their life while the incidence of chronic myeloid leukaemia is higher in them than in the general population

Whether accidents such as blows over the splenic region and fractures play an aetiological part is still uncertain but their occurrence should always be noted even if only for medico-legal reasons

Physical Habitus

It would be a mistake to attach too much significance to external physical characters because we are still profoundly ignorant about the varying susceptibility of different physical types of human beings to various maladies *Even so* the matter is of importance in general

medicine and in association with disorders of the blood For example it is remarkable how often patients with pernicious anaemia have fair prematurely grey hair wide faces and broad chests with wide costal angles In males with this disease the pelvis is quite frequently of the broad almost eunuchoid type while the distribution of body hair is also frequently of feminoid character Addison himself in his original account of pernicious anaemia said the disease occurs in persons of a somewhat large and bulky frame

In congenital haemolytic jaundice (acholuric family jaundice) errors of development are common the most usual being a tower skull This may not be obvious on inspection and may be difficult to detect even by careful palpation It is however usually demonstrable by radiography Many other abnormalities have been described but only two are at all common viz. brachydactyly often affecting only the little fingers and an extraordinary thinness of the tongue

There is perhaps no aspect of clinical haematology to which the general practitioner could contribute so much as to this the general constitutional features of sufferers from blood dyscrasias

Pallor

The most striking manifestation of anaemia is pallor although its absence cannot always be taken as conclusive evidence of a normal level of red corpuscles and haemoglobin Equally its presence is not invariable in anaemic conditions

It is not enough to note that the skin is pale this can be a most misleading sign because there are constitutional differences between people even of the same race sex or age while some conditions that cause pallor do so by some means other than the production of anaemia For instance workers in lead are often pale probably as a result of vaso constriction of superficial arterioles The same is true of some arterio sclerotics Certainly such pallor in lead workers may be present in the absence of poisoning and of anaemia Again the arsenic eaters of Styria whose pallid complexions are locally much admired are notorious for their stamina and health

The colour of the skin of the face is likely to be more misleading than that of the hands (except of heavy manual workers) Indeed examination of the palms with the hands held at about the level of the heart is often very useful because pallor of the thenar and hypothenar eminences is often a very early sign of anaemia while the grooves usually remain fairly well coloured until poverty of the blood becomes extreme Again the tint of the nail bed is a good guide

although now not often available in women because hidden by varnish

Inspection of the mucous membranes is a procedure which should never be omitted although it is far from supplying unequivocal information in every case Thus the fauces of smokers are usually slightly inflamed thus masking the pallor and the conjunctivae may be equally misleading especially in those women who use eye lash dyes while most of the other mucosae are not ordinarily accessible for visual examination

As is well known there are varying tints of paleness of the skin and it is well worth the trouble of training the eye to detect slight *differences which may be of considerable diagnostic significance* Thus the waxy dead white pallor characteristic of severe loss of blood is very different from the sallow pallor which is seen in cases of intermittent loss of blood although it may be identical in shade with that of aplastic anaemia Then there may be pallor with a slightly greenish tinge which was once considered as being pathognomonic of chlorosis but which is still occasionally seen in cases of chronic hypochromic anaemia associated with achlorhydria It should always be looked for by daylight and is most likely to be detectable in the skin under the chin

The sub icteric (lemon coloured) tinge of severe pernicious anaemia must be remembered although it is now rarely seen either because diagnosis has led to early treatment or because without a diagnosis every kind of haematinic treatment has been given a most reprehensible procedure

Advanced leukaemia is often accompanied by a remarkable greyish pallor which resembles but is different from that of malignant cachexia and is less slaty than that of haemochromatosis It somewhat resembles the occasional ochrodermia of tuberculosis

It would be well to mention some examples of pallor which are not due to anaemia (or of pallor greater than can be explained by the diminution of the red corpuscles or haemoglobin) Thus the oedema of sub-acute nephritis is accompanied by pallor although there is little or no true anaemia and conversely anaemia may be quite severe in chronic nephritis but without any noteworthy pallor Of course in mitral stenosis the malar flush and the redness of the lips may mask anaemia and so in other maladies may jaundice cyanosis and any kind of pigmentation of the skin Then again many examples of what appear to be tropical anaemia are nothing more than the pallid appearance of the skin and mucous membranes that develops in many white persons who have lived long in hot climates

In short then it may be said that pallor of the skin and mucous membranes can be a valuable sign of anaemia but that anaemia of considerable severity can be present in the absence of pallor

The Skin

Many useful hints can be obtained from a careful examination of the skin and its appendages

Lack of normal elasticity similar to that found in old age and in wasting diseases is very common in chronic anaemia and is not always due to loss of subcutaneous fat For instance it is often seen in severe untreated cases of pernicious anaemia in which loss of weight is unusual Indeed the return of some degree of cutaneous elasticity is an early clinical sign of efficacious treatment

Petechiae occur in many blood dyscrasias being a direct result of malnutrition of the capillaries by the impoverished blood damage to the endothelium for example by toxins decrease in the number or functional efficiency of the platelets or of minute infiltrations or emboli in the cutaneous vessels

These minute haemorrhagic spots must be carefully inspected in order to obtain all the information possible Thus first petechiae must not be confused with the common de Morgan spots which resemble them in not fading on pressure but which are of no special pathological significance They are not due to haemorrhage but are the result of senile degeneration of elastic tissue in the skin

The telangiectases which are found in the rare inherited abnormality known as the *Osler Weber Rendu disease* (hereditary haemorrhagic telangiectasia) are also very like petechiae but are really more closely allied at least in structure to de Morgan spots They are most commonly found round the lips and on mucous membranes, but no areas are immune Like petechiae they do not completely fade on pressure but unlike them they do not undergo the usual colour changes of effused blood It may be mentioned here that this disease rarely manifests itself before middle age

The distribution of petechiae is important e g they are more likely to involve the hair follicles in scurvy than in purpura haemorrhagica and most other blood diseases

Petechiae may be found on otherwise normal skin or they may be situated on small wheals as in the anaphylactoid purpuras (Henoch s and Schönlein s)

It cannot be too strongly stressed that the recognition of an urticarial component in these latter types of purpura is of the utmost importance in excluding the ordinary blood diseases and in deciding

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may complicate chronic leukaemia First there are certain non specific states often known as *leukaemides* which are not due to infiltration of the skin by leukaemic cells and which may also occur in association with other diseases It is not surprising therefore that the underlying malady is often overlooked because it is not usual to carry out blood examinations in every case of skin disease Secondly there are true infiltrations with leukaemic cells which are commonest in chronic lymphatic leukaemia either forming innumerable small nodules or sometimes large tumours

Among the leukaemides *herpes* is one of the most important because it is a fairly common prodromal sign of chronic lymphatic leukaemia and much less commonly of the myeloid type If films are made of the fluid in the vesicles the typical leukaemic cells can usually be found even when they are very scanty in the blood and oddly enough the cells in the vesicles are often less mature than those in the circulation Absence of such cells from the herpetic fluid is not however sufficient evidence on which to exclude leukaemia

Specific infiltrations take a great variety of forms One of the most remarkable is *erythrodermia* in which there is progressive reddening of the whole body together with a peculiar atrophic and yet thickened condition of the integument (homme rouge) with total loss of hair and some degree of atrophy of sebaceous and sweat glands This state is often accompanied by only slight changes in the blood the usual underlying condition being chronic aleukaemic lymphatic leukaemia For this reason it is well to make a rule to excise a piece of skin for histological examination in suspected cases because for months or even years the changes in the blood may be so slight as to make a diagnosis of lymphatic leukaemia impossible

More *massive leukaemic infiltrations* are perhaps less difficult to recognize clinically although they also tend to be commoner in aleukaemic cases particularly of the chronic lymphatic type. Even when the nature of such masses seems to be obvious it is well to submit a piece for histological examination while films comparable with those of the blood should be made by rubbing the cut edge of the skin on the slide

Skin eruptions are not common in association with other blood diseases but *acne* is a common complication of the iron deficiency anaemia of adolescents

Indolent ulcers over the malleoli fairly commonly develop in cases of chronic splenomegaly This is an almost constant finding in sickle cell anaemia but it is not infrequent in acholuric family jaundice and

whether severe abdominal pain in a child is due to intussusception or to anaphylactoid purpura of the Henoch type It must however be borne in mind that intussusception may develop at the site of a purpuric bleeding into the gut wall

Larger haemorrhages into the skin also occur in a variety of diseases but are on the whole less informative than are petechiae but it is necessary to palpate them carefully to determine whether there is infiltration in addition to bleeding as is commonly the case in leukaemias

If the existence of a haemorrhagic disease is suspected scarcity of cutaneous haemorrhages whether petechial or otherwise must not without further investigation be accepted as indicating that the dis ease is a mild one The underlying pathological process may vary in intensity from time to time and often in mild cases there may be periods during which no spots appear If the history suggests the possibility of a larval form of one of these diseases the degree of capillary permeability should be tested as follows

The forearm is carefully inspected for petechiae and also for any spots which might be confused with them and each one of these is clearly marked with a skin pencil The cuff of a sphygomanometer *is then placed smoothly round the upper arm and is inflated to a* point mid way between the diastolic and systolic pressures It is left at this level for five minutes and the arm is then inspected for new petechiae while a second inspection should be made five minutes later because some petechiae may develop slowly

If a more delicate method is deemed necessary the procedure may be modified Thus after the first part of the test as described above the cuff is again inflated after the inspection at the end of five minutes has been made and it is again left inflated for five minutes In cases in which the tendency to bleeding is a slight one the second test may prove positive when the first did not

Even in normal persons a few petechiae may develop under the cuff but these are of little or no significance while a scanty crop may occur distal to the cuff in healthy women just prior to or more rarely during menstruation Of course the second method of testing is the more likely to reveal such slight tendencies to haemorrhage

Cutaneous eruptions are fairly common in the leukaemias especi ally in the chronic lymphatic type but petechiae are unusual except in primarily acute leukaemias and in the terminal stages of the chronic disease

There are two main groups of dermatological conditions which

the kidneys The motions are normal or dark in colour quite unlike those of the obstructive type

Experience is needed to distinguish the peculiar red colour of patients with *polycythaemia vera* from ordinary cyanosis but once the difference has been appreciated the distinction is fairly obvious

The odd tints of *methaemoglobinaemia* and *sulphaemoglobinaemia* cannot easily be missed once they have been seen but they are impossible to describe

The slaty greyness of the skin in cases of *haemachromatosis* is also very striking and it is no longer quite as rare as it used to be The number of people who have been given large numbers of transfusions is now quite considerable and as there is often some degree of haemolysis after infusion of foreign blood iron is likely to be deposited in the tissues Admittedly pigmentation of the skin by this means is not common but it does occur after repeated transfusions have led to the deposition of considerable amounts of iron in the spleen liver and skin Then again the vogue for intravenous injections of iron could also lead to excessive deposition of the pigment if too many injections are given We have therefore to distinguish haemachromatosis into two types primary and secondary

A few of the rarer cases of pigmentation are worthy of mention Thus patchy pigmentation of the skin has been seen in cases of *aplastic anaemia* and seems to be commonest when the damage has been caused by various synthetic organic hair dyes

Pigmentation is found in quite 50 per cent of *Gaucher s disease* The head neck and palms of the hands are most commonly involved but symmetrical brown discoloration of the legs from the knees to the instep has also been reported A brownish pinguecula is almost pathognomonic of this malady

In the very rare *Hand Schuller Christian disease* the skin may become yellowish brown with small xanthomata sometimes in groups sometimes diffusely scattered Small papules with reddish edges and yellow centres have also been recorded

Brownish pigmentation interspersed with areas of leucoderma (vitiligo) is frequently seen in chronic anaemias especially in *pernicious anaemia* and the *chronic hypochromic* variety In the past pigmentation in pernicious anaemia was often due to the long-continued administration of arsenic rather than to the underlying disease Such pigmentation is still seen in cases of chronic myeloid leukaemia in which arsenic has been administered for a year or two

in chronic myeloid leukaemia Improvement in the patient s general condition does not always affect the ulceration whereas diminution in the size of the spleen is usually followed by healing Thus X ray treatment over the spleen in chronic myeloid leukaemia is often fol lowed by disappearance of such ulcers which leave a thin brownish scar Similarly splenectomy in acholuric jaundice is followed by healing with residual pigmentation

In some cases of splenomegaly areas of pigmentation over the malleoli may be found although no history of previous ulcers can be obtained

Itching is most important especially in Hodgkin s disease in which it may be the earliest complaint pruritus preceding the deve lopment of glandular or splenic enlargement by weeks or months No cutaneous changes other than those due to scratching can be detected in most of these cases Even histological examination does not reveal specific lesions at this stage and the diagnosis can there fore only be made by the subsequent course of the illness Some times such pruritus is accompanied by an increase of eosinophils in the blood This is of course not pathognomonic of Hodgkin s disease but its presence is suggestive

Pigmentation general or local may be significant For example there is the lemon yellow tint of pernicious anaemia which is now rarely seen because treatment is started early A similar tint usually more pronounced is seen in acholuric family jaundice but here the intensity of the pigmentation considerably varies from time to time even without treatment.

Some degree of icteric pigmentation occurs in association with all types of haemolytic disease and because of the clinical difference between icterus of this type and obstructive jaundice some dis cussion is needed

The usual symptoms and signs of the obstructive type of jaundice do not occur or are very much modified in chronic haemolytic diseases Thus although the skin and mucosae are yellow the tint is different and however severe the haemolytic jaundice becomes it never presents the dark green colour so well known in severe cases of the obstructive type Then again there is neither pruritus nor a tendency to bleed as a result of haemolytic jaundice while the ex treme mental depression associated with the obstructive variety is absent Bradycardia is not part of the picture of chronic haemolytic jaundice as it is of obstructive jaundice

The urine is not dark in haemolytic jaundice because haemo bilirubin which has not passed through the liver is not excreted by

affects all the papillae of the dorsum and the edges of the tongue leaving a smooth bald appearance * As a rule the atrophic process only extends back as far as the circumvallate papillae but in severe cases even these may become strikingly reduced in size

It is of the utmost importance to realize that efficient treatment of the anaemia will after a variable but usually long time lead to re formation of papillae Such recovery of the structural changes in the tongue is a much slower process than is restoration of the blood to normal It is not known whether the improvement is due to better nutrition of the papillae or whether liver extracts supply some specific factor

In a case of pernicious anaemia under treatment the appearance of the tongue should become normal within twelve months If it does not do so even although the blood is normal the dose of liver extract should be increased As pernicious anaemia is a deficiency disease it should not be regarded as having been completely con trolled unless *all* the clinical and haematological abnormalities have disappeared

In *chronic hypochromic microcytic anaemia* soreness of the tongue is also common but neither the patient s complaints nor the ob jective signs are as striking as in pernicious anaemia Further it is also common for the complaints of soreness to precede the onset of clinical anaemia Furring is usually slight and the tongue often has a red beefy appearance while the papillary atrophy so characteristic of pernicious anaemia is either absent or slight Fissures at the angle of the mouth are quite common and are often attributable to a con comitant deficiency of riboflavin

Dysphagia is fairly common and seems to be most troublesome in the cases that have the most severe lingual changes As a rule this dysphagia disappears when the anaemia is relieved by treatment There are however cases in which difficulty in swallowing is really severe and this may be the presenting symptom (*Plummer Vinson syndrome*) In this condition the difficulty in swallowing may be diminished but is not cured by relieving the anaemia and indeed even in well treated cases the development of post-cricoid carcinoma is fairly common

The abnormal thinness of the tongue in some cases of *acholuric family jaundice* has already been mentioned but this does not cause any discomfort

Soreness of the mouth and tongue is of course a well known symptom in *sprue* Here it is not directly associated with the intensity

* Small purple varicosities often develop on the smooth edges

The Hair

Loss of lustre of the hair often associated with brittleness is usual in all forms of chronic anaemia but is less marked in the haemolytic types Indeed it is uncommon in acholuric family jaundice

Early greyness is almost invariable in pernicious anaemia some times as a family characteristic although not all the members of the family develop pernicious anaemia In other cases the only member of the family to go grey early is the one in whom pernicious anaemia later develops

A similar tendency to early greyness is found in chronic hypochromic anaemia its incidence being highest in those families in which cases of both pernicious and chronic hypochromic anaemia occur

It is also striking that pernicious anaemia is much less common in dark haired persons than in blondes

Increased thickness of the hair sometimes with hirsuties is part of Cushing s syndrome which is often accompanied by erythrocytosis

The Nails

A diminished rate of growth sometimes accompanied by longi tudinal ridging and brittleness occurs in many chronic anaemias but the well known spoon nails (koilonychia) are almost pathognomonic of chronic hypochromic microcytic anaemia

The Tongue

It is still the custom to look at every patient s tongue but this has regrettably become almost a meaningless ritual The careful classi fications of the older school of physicians have to a great extent been forgotten and as a result far less information is obtained by this means than should be the case

In *pernicious anaemia* the condition of the tongue is especially interesting and important As is well known soreness of the tongue is a common complaint this may be more or less continuous or it may occur only when hot or spicy foods are taken Even in the early stages there may be a history of recurrent small ulcers at the tip or edges of the tongue and indeed this may precede all other signs of anaemia by weeks or even months

Usually the tongue is strikingly clean with no trace of furring even far back on the dorsum Except in the very earliest cases some atrophy of the papillae can be detected usually most strikingly at the edges of the organ In severe cases and in those that have not re ceived treatment until long after the onset of the disease the atrophy

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of the anaemia and is likely to be quite as severe in the cases with hypochromic anaemia as in those of the hyperchromic type

Furring of the tongue is of course a usual finding in association with *carcinoma of the stomach* This is a common cause of anaemia in the middle aged and the presence of furring of the tongue serves at least to some extent to differentiate it from pernicious anaemia

The development of a furred tongue in a sufferer from pernicious anaemia should always arouse suspicion of the intercurrent development of carcinoma of the stomach It is uncertain whether the incidence of gastric carcinoma is higher than normal in patients with pernicious anaemia but there is some reason for thinking that this is so

Severe infective and necrotic lesions of the tongue may occur in association with *acute leukaemia* and *agranulocytosis*

The Mouth and Fauces

The presence of gross infection of the buccal gingival and faucial mucosa should arouse suspicion of the presence of a blood disorder more commonly than it does In fact except in the most transient oral and faucial infections blood examination should be regarded as an essential part of the investigation Even if all that is found as a result of such an examination is the presence of a simple leucocytosis it will have been important because it will be clear that one is dealing with some ordinary type of infection On the other hand in all states in which the granular leucocytes of the blood are reduced to low figures there is a great liability of infection of the oral cavity *agranulocytosis* whether spontaneous or due to drugs is an outstanding example of such an occurrence but in *acute leukaemia* an identical clinical condition may occur even if the number of white cells in the blood is high because the majority are immature and abnormal forms which are of no value as a defence against infection

In *agranulocytosis* the oral lesion is almost purely necrotic whereas in *acute leukaemia* large or small nodular infiltrations and haemorrhages may be found in addition to signs of infection

Bleeding into and from the *buccal mucous membrane* not accompanied by infection may occur in any type of haemorrhagic diathesis and it is especially common in *thrombocytopenic purpura* although apart from the presence of haemorrhages the mucous membranes look normal In *scurvy* on the other hand bleeding occurs from the gums which are always spongy and usually infected

The condition of the *tonsils* should also be investigated They may be strikingly large in cases of *lymphatic leukaemia* particularly the

chronic form and these may often be found when there is no obvious local infection and even before there is any generalized enlargement of the lymphatic glands of the spleen It is important to recognize this possibility because a chronic leukaemia may suddenly become acute after tonsillectomy just as it may after tooth extraction

The Spleen

Some degree of splenomegaly is common in association with many blood dyscrasias and details will be found in the appropriate sections Here all that is necessary i a brief account of the methods of examination of the organ

Palpation of masses in the left hypochondrium is not always as simple as one might expect

If a spleen of normal shape becomes enlarged the lower pole will travel downwards and to the right thus reaching the navel and later the right iliac fossa At the costal margin it will not be possible to find a limit of the mass because the organ extends behind the ribs where its size can only be determined by percussion If in addition to these characters a notch can be felt on the right hand edge of the down growing mass there can be little doubt that it is the spleen

Sometimes however the shape of the spleen is initially abnormal so that as it enlarges it passes almost straight down the left side of the abdomen reaching the left iliac fossa Of course at the same time its transverse size also increases and its right hand edge may reach to or pass beyond the navel here again if the notch is palpable there can be little doubt as to the nature of the mass

Rarely a greatly enlarged left hepatic lobe may closely simulate splenomegaly and occasionally only radiography can decide the nature of the mass Sometimes it is useful to distend the stomach with gas in order to obtain a clear picture of the spleen

Palpation of the spleen should include an assessment of the mobility of the organ which depends mainly upon the presence or absence of adhesions The mass should therefore be gently moved and in addition any displacement due to change of position e g lying on the right side or in the knee-elbow position should be noted

The question of the mobility of the spleen is important in cases in which splenectomy may be necessary because in this way it is possible to gain some idea of the difficulties that may be encountered at operation

In cases in which a mass in the left hypochondrium is small or perhaps is only suspected every possible manoeuvre should be tried

Not only should the abdomen be carefully palpated with the patient lying prone while every attempt is made to cause adequate relaxation of the abdominal wall e g by requesting the patient to press his head firmly against the pillow while he slowly breathes in and out but it is of course necessary to try and feel the mass while the patient is lying in various positions and with care and skill even slight enlargement of the organ can be detected Sometimes palpation in the knee elbow position solves the problem Percussion may help in cases of doubt and is always useful for determining the upper limit of the mass If all these methods of examination are used one can usually determine with certainty whether or not the spleen is enlarged

In some cases the splenic nature of a mass in the left hypochon drium can be proved by observing diminution of its size after a sub cutaneous injection of adrenalin

Auscultation over a distinctly enlarged spleen may reveal a sys tolic murmur This is a useful finding because if such a murmur is heard it is almost certain that the palpable mass is neither an en larged left hepatic lobe nor a spleen which has been pushed forward by for example a retro peritoneal growth

The presence of a to and fro murmur synchronous with respira tion is proof of perisplenitis which is usually due to infarction such as is a common complication in chronic myeloid leukaemia

Spleen puncture is a procedure that can be employed in suitable cases and the results will be mentioned in the appropriate sections of this book All that need be said here is that the operation is potentially dangerous and that it should therefore always be done by one with experience of the technique

The Liver

Enlargement of the liver without concomitant splenomegaly is uncommon in blood diseases It does however occasionally occur in Hodgkin s disease as a result of diffuse or nodular infiltration It may also be found in acute leukaemia particularly in the monocytic type

Enlargement of both liver and spleen occurs in many blood diseases For example in chronic haemolytic anaemias such as acholuric family jaundice some degree of hepatomegaly sooner or later develops although of course enlargement of the spleen pre cedes this often by many years Then again in such rare conditions as Gaucher s disease infiltration of the liver may lead to considerable increase in size but this occurs only in the later stages that is to say long after the spleen has become enormous

Lymphatic Glands

Enlargement of lymphatic glands is a frequent concomitant of disorders of the blood and may be generalized or confined to a few groups The order in which lymphadenopathy develops is often very significant because there are almost constant differences in the evolution of the various diseases For example enlargement of axillary glands developing before any other groups is more likely to be due to chronic lymphatic leukaemia than to Hodgkin s disease On the other hand involvement of cervical glands before any others is common in Hodgkin s disease although of course such isolated enlargement may be due to many other causes e g oral sepsis Then again early enlargement of the epitrochlear glands is quite common in syphilis and may occur weeks or months before generalized lymphadenopathy develops

Careful palpation of enlarged glands may give much useful information Thus the peculiar rubbery consistence of the glands in Hodgkin s disease is very different from the hardness of glands that are the seat of carcinomatous infiltration while the elastic consistence of the glands in chronic lymphatic leukaemia is almost pathognomonic of that disease

Then again there is the question whether the glands are adherent to one another and to surrounding structures and of at least equal importance whether they are tender on pressure or are spontaneously painful Of course in every case of lymphadenopathy examination must be made to determine whether there is any lesion in the area of drainage that might account for the enlargement and it is not only necessary to search for frankly septic foci because quite slight lesions may be associated with glandular enlargement as for example the redness of the fauces in glandular fever while a rash may indicate the presence of rubella In short the investigation of enlarged lymphatic glands demands a detailed clinical examination while bearing in mind that many of the causes belong to the field of general medicine rather than to that of haematology

Reproduction

Amenorrhoea is a classical symptom of anaemia which is almost invariable in chlorosis It is however almost as common to be given a history of menorrhagia Obviously such profuse menstrual loss can cause post haemorrhagic anaemia whether it be due to some gynaecological abnormality or to some blood disease such as thrombocytopenic purpura What is however less widely realized is that menorrhagia may itself be a sign of anaemia especially of the chronic

hypochromic variety and many a curettage has been performed on women who have only needed to take large doses of iron by mouth

In all chronic anaemias there is diminution of fertility in women and usually a reduction of libido in both sexes Impotence may develop in the male although it is to be remembered that priapism is a classical although uncommon sign of chronic myeloid leukaemia in which it may be the initial complaint

The testes do not usually show any clinical abnormalities in blood diseases but leukaemic infiltration either unilateral or bilateral does occasionally occur A little blood may be mixed with the semen in thrombocytopenic purpura of both primary and secondary type

The Eyes

Pallor of the conjuctivae is a classical sign of anaemia but its absence is not to be regarded as proof of the absence of anaemia because the slightest degree of conjunctivitis will mask the pallor

The sclera often reveals the slighter degrees of icterus and may indeed be the only site in which it can be recognized in very mild cases of haemolytic anaemia

A brownish pinguecula is characteristic of Gaucher s disease

The ophthalmoscope is almost as indispensable to the haematologist as it is to the neurologist because changes in the fundus are of great diagnostic significance Thus in haemorrhagic diseases the occurrence of retinal haemorrhages may lead to blindness while in association with slighter degrees of thrombocytopenia the eye grounds may be the only place in which haemorrhages can be detected (Plate II figs 5 and 6)

In the leukaemias retinal haemorrhages whether alone or accompanied by infiltrations and leukaemic deposits are quite common particularly in the acute stages (Plate III figs 7 and 8)

The common subjective symptoms of anaemia such as spots in front of the eyes and dimness of vision are not usually accompanied by detectable organic changes

The Urine

Examination of the urine should never be omitted Slight albuminuria is common in severe anaemias and may accompany chronic leukaemia especially the chronic myeloid form

Great care should be taken in the examination for albumen in order that Bence Jones protein if present is not missed It should

be remembered that this substance is precipitated at a temperature of about 60 or less and redissolves when the urine boils being again precipitated as it cools to about 60 disappearing when it becomes completely cold Although the presence of Bence Jones protein is not absolutely pathognomonic of myelomatosis its presence should always arouse great suspicion of this disease

Examination of the urinary deposit should not be omitted In some chronic haemolytic anaemias particularly in nocturnal haemoglobinuria haemosiderin is continuously present in the deposit while in conditions of less constant haemolysis it can be found intermittently and usually in smaller amounts

In the leukaemias the characteristic immature and abnormal cells more or less lysed are always present in the urinary deposit and on occasions a diagnosis has been made by this means at a time when other clinical signs were equivocal

Casts may be present in any type of blood disease as a result of associated nephritis but structureless ones are present in many cases of myelomatosis and if found are diagnostic of the disease

Circulatory System

A presenting symptom in many cases of anaemia is palpitation This is often associated with tachycardia but it may be due to simple increase of arterial pulsation even when the pulse rate is not increased The pulse pressure is often increased and if the anaemia is severe it is sometimes possible to detect capillary pulsation in the lips and finger tips

Precordial pain either spontaneous or on exertion may closely simulate angina especially in cases of severe anaemia in the elderly For some unknown reason such anginal pain is commoner in pernicious anaemia than in the hypochromic types

Signs of congestive cardiac failure may occur in any type of anaemia This is frequently only slight and is manifested by oedema round the ankles It is commoner in pernicious anaemia than in other type anaemia

A systolic bruit is commonly audible being usually best heard at the second pulmonary interspace although it may be audible all over the precordium It is only in cases of sickle cell anaemia that there is any real likelihood of the murmurs being confused with those of organic heart disease

A humming sound detectable over the cervical vessels (bruit de diable) is common in all severe anaemias but seems to be most marked in the chronic hypochromic types

Respiratory System

It is probably true to say that the commonest presenting symptom of anaemia is dyspnoea on exertion This is often almost very strik ing but apart from this symptom it should be noted that in cases of intense anaemia breathing is strikingly shallow even when the patient is at rest

Anaemia itself is not the cause of any abnormal physical signs in the lungs but any enlargement of the spleen however caused may result in impairment of air entry at the left base where there is sometimes although rarely a small effusion in such cases

Neuro-muscular System

Headache giddiness faintness tinnitus black spots in front of the eyes irritability and lack of power of mental concentration are common complaints in all forms of anaemia they are of course due partly to anoxia of the nervous system and partly due to muscular imbalance As a rule there is increased sensitivity to cold but in the *leukaemias in which the metabolic rate is characteristically increased* there is dislike of hot weather

Gastro intestinal System

No specific symptoms occur in blood dyscrasias but in pernicious anaemia before treatment alternating constipation and diarrhoea are common

The large malodorous stools of sprue are of course well known

The possibility of infestation by intestinal helminths should be borne in mind in cases of any anaemia of obscure aetiology especi ally of course if there is eosinophilia in the peripheral blood

The onset of diarrhoea in the course of the leukaemias and in Hodgkin s disease often indicates the presence of infiltrations of the intestinal mucous membrane

Metabolism

Anaemia itself does not necessarily cause loss of weight Indeed in pernicious anaemia Addison said the bulkiness of the general frame and the obesity often present a most striking contrast to the pallor and exhaustion observable in every other respect It must not however be assumed that loss of weight excludes the diagnosis of pernicious anaemia because as in all other forms of anaemia malnutrition may become very noticeable

In leukaemias especially the acute forms loss of weight is usually rapid but in chronic cases nutrition is often well maintained until

the late stages It should be borne in mind that some decrease of weight may follow radiotherapy especially in chronic myeloid leukaemia mainly perhaps as a result of decrease in size of the spleen When such treatment is successful the lost weight is however rapidly regained because the previously elevated basal metabolic rate returns to a more normal level

Slight irregular pyrexia is common whenever anaemia is severe but a distinct febrile reaction develops when rapid blood destruction occurs e g in exacerbations of acholuric family jaundice

The Skeleton

Changes in the structure of the bones occur in association with many blood disorders and will be described in the appropriate sections As a rule they do not cause clinically striking signs except in some cases of myelomatosis in which tumour like masses and spontaneous fractures may develop The only other skeletal change that can commonly be appreciated by clinical examination is tenderness on pressure over the sternum usually only over the lower third This is a peculiar condition because it is patchy and unless the whole surface of the bone is carefully examined by pressure with the finger tip it can easily be overlooked Even more peculiar is the fact that such tenderness may not be revealed by percussion even when it is extreme on pressure

Sternal tenderness is not pathognomonic of the leukaemias although it is much commoner in these diseases than in any others Probably it results from pressure of actively proliferating cells on the anterior plate of the bone and it is not surprising therefore that it may also be found in association with any actively regenerative process e g during exacerbations of acholuric jaundice and in other haemolytic anaemias

CHAPTER II

SIGNS OF BLOOD DISEASFS (HAEMATOLOGICAL)

IT has already been pointed out that this book is intended for the general physician and practitioner For this reason only the essentials of laboratory investigations and reports will be described so that a general idea of the principles of interpretation can be obtained More detailed interpretations will be found in the appro priate sections

An enormous literature has grown up in connexion with the blood cells and their variations quantitative and qualitative in various diseases but here only an outline will be presented

Just as it is possible to treat a case of diabetes competently without a detailed knowledge of the finer points of the metabolism and bio chemistry of the carbohydrates and fats so it is possible to deal with many perhaps most of the dyscrasias of the blood if certain basic principles are clearly apprehended True enough the expert may be needed in the early stages of these cases both in order to assist in making a diagnosis and in suggesting the best methods of treatment

Investigation of the Blood and Blood Forming Organs

The blood is not produced in the circulation the sites of the con tinuous production and destruction of its cells are the haemopoietic organs namely the bone marrow the lymphatic glands the spleen and to a less extent the liver

In normal post natal life it is the bone marrow which plays the main part in the production of blood cells indeed the only part in the production of granular leucocytes and red cells most of the monocytes being produced in the spleen and the remainder of the reticuloendothelial system while lymphocytes also present in the marrow are far more numerous in the lymphadenoid organs where the majority of them are formed

Once the existence of a disorder of the blood is suspected a series of further investigations becomes essential although not all the avail able methods are necessary in every type of case

As a rule examinations of the peripheral blood enable sound



FIG 2 (*b*)—Hiatus hernia Taken in the prone position clearly showing the presence of a small portion of stomach protruding through the diaphragm alongside the oesophagus

inferences to be drawn as to the functional state of the haemopoietic organs In this connexion the most important steps are enumeration of the red corpuscles estimation of the amount of haemoglobin enumeration of the white cells and assessment of the number of platelets Further in every case a more or less detailed examination of the various types of cells must be carried out on stained films

By these means the existence of anaemia or polycythaemia and of leucocytosis or leucopenia is readily appreciated while examination of stained films permits of the detection of quantitative and qualitative changes in the different types of white cells Similarly enumeration of the platelets may throw some light on abnormalities of bleeding and coagulation

Various chemical examinations are of importance in haematology e g icterus index plasma proteins etc but these special methods need only be employed in particular cases which will be discussed in the appropriate sections

Obviously examination of the peripheral blood can only enable one to draw inferences as to the state of the formative organs but such inferences are of course subject to inaccuracy There may for example be some disorder in the emigration of cells from the haemopoietic organs into the blood so for example the blood picture (*haemogram*) may resemble that of aplastic anaemia when in fact the formative organs are active (p 114)

Clearly then direct examination of the individual formative organs can be of great value

Bone Marrow

Puncture of the sternum is the commonest method of obtaining marrow for cytological examination but other bones can also be punctured As a rule it matters little which bone is punctured because the whole of the marrow in the body is in the same functional state The sternum has however the advantage of being easily accessible and having a thin anterior plate

In every case films should be made from the material obtained by marrow puncture and in addition histological sections should be made

The former procedure enables the percentage of the different types of cells to be ascertained while abnormalities of structure are relatively easily recognized e g asynchronism in the maturation of cytoplasm and nucleus the presence of cell inclusions etc The histological method however gives a better insight into the degree

of cellularity of the marrow and may also be the only method available for demonstrating infiltrations These may be too tough to be spread out in films and can therefore be overlooked if the histological method is not also employed

The normal myelogram is as follows but it must be realized that considerable variations consistent with health occur

Leucocytic series	per cent
Myeloblasts	1 0– 2 4
Promyelocytes	1 0– 3 0
Neutrophil myelocytes (half mature)	4 0– 9 0
Neutrophil myelocytes (mature)	4 0– 9 0
Neutrophil metamyelocytes	1 0– 4 0
Neutrophil staff forms	rare
Neutrophil polymorphs	40 0–50 0
Eosinophil myelocytes	0 2– 1 0
Eosinophil polymorphs	1 0– 4 0
Basophil myelocytes	rare
Basophil polymorphs	*0 1– 1 0*
Lymphocytes	7 0–16 0
Monocytes	2 0– 9 0
Plasma cells	0 3– 1 0
Reticulum cells	a few
Megakaryocytes	a few
Erythrocytic series	
Pro erythroblasts	0 5– 3 0
Normoblasts	5 0–15 0

Some unidentifiable cells are also found but the greater the experience of the observer the smaller the percentage

The proportion of nucleated red cells to white cells is normally about 1 3 Gross variations are significant

The Spleen

*Investigation of the functional activity of the spleen is a time-con*suming procedure which is briefly discussed in the chapter on hypersplenism

Spleen puncture can however reveal cytological changes in the

same way as can marrow puncture but the procedure cannot be employed in every case and indeed should not be attempted on a spleen of normal size The operation should never be done in cases of haemorrhagic disease

The normal splenogram is as follows

	per cent
Reticulum cells	0 5– 2 0
Erythroblasts	0 1– 0 2
Myelocytes	0 1– 0 5
Polymorphs	5 0–15 0
Eosinophils	0 2– 1 0
Monocytes	1 0– 3 0
Lymphoblasts	very scanty
Lymphocytes	60 0–90 0
Plasma cells	0 0– 1 0

Far more detailed sub-divisions have been published but fortunately in many cases careful inspection of films by an expert suffices even without a differential count

It may be said that the types of splenic change can be grouped as follows

(*a*) Lymphatic reaction such as is seen in lymphatic leukaemia

(*b*) Myeloid reaction which is seen most distinctly in chronic myeloid leukaemia but which also occurs in association with various anaemias for example gross encroachment on the marrow by osteosclerosis will lead to enlargement of the spleen which is due to compensatory myeloid reaction

(*c*) Erythroblastic reaction which forms a part of ordinary myeloid metaplasia but also occurs in almost pure form in the rare Di Guglielmo s disease

(*d*) Macrophage reaction Here there is much increase of monocytes and phagocytic cells leading to increased size of the spleen This is a type of change that occurs in such diseases as chronic malaria and chronic haemolytic conditions

(*e*) Infiltrative conditions Spleen puncture may reveal the presence of large pale cells e g Gaucher s cells Less commonly the typical giant cells of Hodgkin s disease may be found while in the acute leukaemias the infiltrating cells although resembling the parent cells of the blood present abnormalities of structure

(*f*) Megakaryocyte reaction As an isolated phenomenon this is extremely rare but an increase of megakaryocytes *sometimes a* striking one is a common feature of myeloid metaplasia

Gland Puncture

The functional state of the lymphatic glands varies from time to time and place to place For this reason gland puncture cannot be regarded as throwing a great deal of light on the functional condition of the lymphadenoid tissue in general It is however a valuable procedure in the diagnosis of such maladies as Hodgkin s disease chronic tuberculosis malignant infiltrations etc

It is *impossible to give figures for a normal adenogram because* the functional (and therefore also the structural) state varies greatly from group to group and from time to time An assessment of the predominant cell types and of the presence of abnormal cells suffices for diagnosis in many cases of lymphadenopathy

Liver Puncture

This procedure is not without danger and is very rarely indicated in diseases of the blood It may however be the only means of making a diagnosis in early cases of chronic aleukaemic leukaemia parti *cularly the lymphatic type*

Blood Coagulation

A very large number of methods is available and only a few general principles will be discussed here

Various methods of estimating the coagulation time are employed but it must be realized that if the result shows a deviation from nor mal further investigation is immediately called for because a number of factors on which coagulation depends is large

The bleeding time depends upon two main factors viz the per meability of the capillaries and the number of blood platelets In every case of haemorrhagic disorder this simple method of investiga tion should be employed but little attention should be paid to slight variations

It must be emphasized that in every haemorrhagic disease it is not sufficient to carry out quantitative examinations The structure of *the blood platelets for example may be as important as their number*

Other methods of examination of the plasma have only limited application in haematology and will be discussed in the appropriate places e g the Paul Bunnell reaction the fragility of the red corpuscles etc

At the end of this chapter will be found the normal figures a knowledge of which is essential for the interpretation of the variations found in disease

A scheme of the development of the various cells found in the

circulation in health and disease is shown rather diagrammatically in Figure I the general principles of which should be mastered if a reasonable understanding of the subject is to be attained

Red Cells

In health there is little variation in the shape or size of the red corpuscles which are biconcave non nucleated discs about 7 2 microns in diameter But in all conditions in which there is increased formation of red corpuscles in the bone marrow variations in size are found This condition *anisocytosis* may be of two types thus the average diameter may be less than normal i e *microcytosis* or it may be greater than normal i e *megalocytosis* (macrocytosis) * Corpuscles larger or smaller than normal are not necessarily im mature but their presence in the blood is indicative of unduly rapid formation of red corpuscles Even so the two states do indicate different types of response megalocytosis is an indication that there is a deficiency of haemopoietic factor in the body while microcytosis is most commonly due to iron deficiency

Slightly more pathological is the presence in the blood of corpus cles of bizarre shapes (*poikilocytosis*) e g pyriform or grossly ir regular Such a state is also indicative of an unduly rapid formation of red corpuscles but usually indicates that there is in addition some abnormality of the marrow thus poikilocytosis although not pathognomonic of pernicious anaemia is most marked in the anaemias of this type i e those due to deficiency of haemopoietic factor (*vide* Chapter IV)

Some anomalies of shape are however characteristic of special disease processes For instance in acholuric family jaundice the red corpuscles as seen in films appear to be smaller and darker than normal This is due to their being spherical instead of discoid and such *spherocytosis* is characteristic of chronic haemolytic anaemias being most striking in the familial type Then again in *sickle cell* anaemia the red corpuscles present a falciform appearance which may not be recognizable in direct films but which develops when the blood is kept for a time in an atmosphere with a reduced oxygen tension

Normal red corpuscles have a well stained edge and a pale centre the pallid area corresponding to the thinnest part of the disc Now as the red colour depends upon the amount of haemoglobin it fol lows that decrease in the amount of this pigment will result in an increase in the size of the central area (*hypochromia*) and this may

* The difference between macrocytes and megalocytes are given on page 66

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demand for red cells or as a result of irritation of the marrow for example by deposits of tumour-cells

The above description applies to the normal process of formation of red corpuscles but when there is deficiency of haemopoietic factor (p 66) a different process occurs (*megaloblastic blood formation*) This is briefly described on page 66

The mature red corpuscle is of course not a complete cell as the nucleus has been lost It possesses neither long life nor the power of reproduction The present view is that the maximum life span of the red corpuscle after it leaves the bone marrow is in the region of one hundred and twenty days There is thus throughout life continuous formation of new red corpuscles in the bone marrow and destruction at the periphery The exact mode of destruction of effete red corpuscles is still uncertain but from a practical point of view this is perhaps of little importance What has to be realized is that this apparently extravagant method of maintaining the constancy of the red corpuscles is in fact an example of biological economy Thus the haemoglobin which is set free is immediately broken down into a compound containing iron which is used over and over again in the bone marrow in the process of building up new haemoglobin while the other moiety which is iron free is known as bilirubin This is transported to the liver where it undergoes some chemical modification after which it is excreted in the bile where it plays its well known physiological part in the digestion of fats etc Thus bilirubin has not exhausted its haematological usefulness because it has been shown that it plays an important part in the absorption and utilization of iron

Examples of the interpretation of blood counts will be found scattered throughout the book in appropriate places

Leucocytes

The individual types of white cells differ from one another in structure and function and their variations both in number and quality can give diagnostic and prognostic indications

The *neutrophils* (commonly called *polymorphs*') are cells with a remarkable power of phagocytosis mainly of very small particles such as bacteria and it was for this reason that they were called *microphages* Oddly enough polymorphs are much more active in removing cocci than bacilli and it is therefore not surprising that they increase in number in response to many of the infective diseases due to cocci and if suppuration occurs it is the polymorphs that become the pus cells

be so severe that only the edge of each corpuscle is pink (pessary corpuscle)

It must be realized that the normal corpuscle is saturated with haemoglobin and if the average haemoglobin-content of the cor puscles is above normal (*hyperchromia*) this can only be due to an increase in their average size (*macrocytosis* or *megalocytosis*) Thus an anaemia in which the colour index is above 1 0 (*hyperchromic anaemia*) must also be macrocytic or megalocytic but the converse does not necessarily follow because in the presence of iron deficiency a macrocytic or a megalocytic anaemia can be hypochromic On the other hand microcytic anaemias must always be hypochromic while hypochromic anaemias may be normocytic macrocytic megalocytic or microcytic

Even in health a very small proportion of the red corpuscles in the circulation show signs of being slightly immature they stain slightly bluish (*polychromasia*) instead of the usual pink colour It is how ever difficult to recognize slight variations of tint with certainty and it is therefore better to use the method of vital staining By this procedure slightly immature red corpuscles are shown to contain a fine net work which is easily detectable under the microscope so that the exact percentage of these immature elements can be deter mined Obviously an increase of such *reticulocytes* indicates that very active formation of new corpuscles is going on The value of reticulocyte counts in greatest in the early stages of the treatment of pernicious anaemia (p 69) when their presence in adequate numbers is indicative of response to a preparation containing enough haemo poietic factor

The red corpuscles during normal post natal life are formed only in the bone marrow where they arise from cells containing nuclei (*normoblasts*) If the process is traced backwards from the red corpuscle it will be found that the cell immediately preceding the reticulocyte is one with a dense nucleus in which no structure can be detected Less mature is a similar cell in which the nuclear structure resembles a cart wheel while the cytoplasm is polychromatic i e not filled with haemoglobin Then the least mature cell of this erythropoietic series has dark blue cytoplasm and a rather coarsely mottled nucleus The process of maturation is thus accompanied by increasing density of the nucleus progressive pinkness of the cytoplasm and decrease in the size of the cell until the nucleus is lost and the ordinary red corpuscle is formed

Nearly all these stages may be found in the circulating blood in pathological conditions either as a response to greatly increased

demand for red cells or as a result of irritation of the marrow for example by deposits of tumour-cells

The above description applies to the normal process of formation of red corpuscles but when there is deficiency of haemopoietic factor (p 66) a *different process occurs (megaloblastic blood formation)* This is briefly described on page 66

The mature red corpuscle is of course not a complete cell as the nucleus has been lost It possesses neither long life nor the power of reproduction The present view is that the maximum life span of the red corpuscle after it leaves the bone marrow is in the region of one hundred and twenty days There is thus throughout life continuous formation of new red corpuscles in the bone marrow and destruction at the periphery The exact mode of destruction of effete red corpuscles is still uncertain but from a practical point of view this is perhaps of little importance What has to be realized is that this apparently extravagant method of maintaining the constancy of the red corpuscles is in fact an example of biological economy Thus the haemoglobin which is set free is immediately broken down into a compound containing iron which is used over and over again in the bone marrow in the process of building up new haemoglobin while the other moiety which is iron free is known as bilirubin This is transported to the liver where it undergoes some chemical modification after which it is excreted in the bile where it plays its well known physiological part in the digestion of fats etc Thus bilirubin has not exhausted its haematological usefulness because it has been shown that it plays an important part in the absorption and utilization of iron

Examples of the interpretation of blood counts will be found scattered throughout the book in appropriate places

Leucocytes

The individual types of white cells differ from one another in structure and function and their variations both in number and quality can give diagnostic and prognostic indications

The *neutrophils* (commonly called *polymorphs*) are cells with a remarkable power of phagocytosis mainly of very small particles such as bacteria and it was for this reason that they were called *microphages* Oddly enough polymorphs are much more active in removing cocci than bacilli and it is therefore not surprising that they increase in number in response to many of the infective diseases due to cocci and if suppuration occurs it is the polymorphs that become the pus cells

Increase in the number of leucocytes (*leucocytosis*) in *coccal infections* is due to increased activity of the marrow and it is not surprising that the supply of mature polymorphs may fail to meet the demand there will then be found some neutrophils rather less mature than polymorphs A *shift to the left* is thus indicative of an active marrow responding to the demands made on it, although with a little difficulty the significance of a shift to the left in infections is therefore comparable with that of reticulocytosis in anaemias Clearly the intensity of the response can to some extent be judged by the degree of immaturity of the cells that emerge from the marrow Thus if metamyelocytes are found in the blood it is probable that the strain on the marrow is less severe than if many myelocytes are present Examples of interpretation of blood pictures in infective conditions are given in Chapter 20

The amount of information that can be obtained from careful examination of the neutrophils in infective diseases is really very great and in difficult cases it never suffices to know only the total number of white cells per cubic millimetre and the percentage of neutrophils more delicate observations are essential Thus not only must signs of immaturity of the neutrophils be looked for but the structure of the individual cells must be considered

Just as polymorphs that have become pus cells show signs of degeneration so in severe infections do the neutrophils in the blood Thus the granules may become unduly dark (*toxic granulation*) the nuclei may be denser than normal and there may be vacuoles in the cytoplasm

In overwhelming infections in which the marrow is so damaged as to be unable to respond adequately there will be little or no increase in the number of neutrophils in the blood but there will nevertheless be changes in these cells e g degenerate forms and perhaps immature cells

It cannot be too strongly emphasized that it is untrue to suppose that the height of the white cell count is in itself an indication of the degree of severity of an infection or of the presence of suppuration It is far more from the *quality* of the leucocytes than from their absolute numbers that inferences can be drawn It is therefore always insufficient to ask for a leucocyte count without at the same time demanding a detailed differential examination in which special attention must be paid to the degree of immaturity of the cells and to the presence or absence of degenerate forms

Even with a knowledge of these first principles errors are likely unless interpretations are based on a sound knowledge of the natural

history of the blood-changes in disease Thus although there is no series of blood pictures that is really pathognomonic of various infections there are particular groups of blood changes that are specially likely to be found in average cases For this reason Chapter 20 is devoted to descriptions of symptomatic blood changes i e to an account of those blood pictures that are common in different diseases which are not themselves at least primarily affections of the haemopoietic organs

The neutrophils are the elements which typically react to infections by cocci but in *infections with bacilli* they do not as a rule increase indeed they may diminish in number Thus in such a disease as typhoid fever there is reduction in the total number of white cells (*leucopenia*) with increase either relative or absolute of lymphocytes although the neutrophils may show degenerative and regenerative changes i e they obviously play some part in the vital response Indeed such a complication as perforation of the intestine is followed by a prompt increase in the number of neutrophils

In health the life of a polymorphonuclear leucocyte in the blood is only three to five days

The *monocytes* which are phagocytic elements capable of ingesting larger particles than bacteria and are therefore known as *macrophages* are found in increased numbers of many diseases due to infection by protozoa Sometimes indeed the parasite itself (or some of its products) may be found lying inside these cells

The *eosinophils* the function of which is still uncertain are found in increased numbers in most diseases associated with sensitivity to foreign proteins

Basophils are always scanty in the blood and little is known about them Evidence is however accumulating that they either form or at any rate carry heparin

Platelets play an essential part in the process of coagulation Decrease in their number (*thrombocytopenia*) is associated with a tendency to bleeding whereas excess may lead to thrombosis These facts are of great practical importance especially in connexion with contemplated surgical operations For example splenectomy is almost always followed by increase in the number of platelets (*thrombocytosis*) If then they are present in normal numbers before the operation they may rise so high after it as to lead to widespread thromboses This possible danger should always be borne in mind when deciding on the treatment of such conditions as acholuric jaundice and Banti s disease

The duration of life of the platelet varies greatly because unlike

the red cell once it has performed its function it disappears but it seems that on the average its duration of life is two to four days

Plasma

It is only in recent years that the chemical and physiological changes in the blood plasma and serum have become of importance in haematology

The most significant changes are those which are found in the plasma proteins (albumin and globulin) and these are particularly significant in those diseases in which plasma cells are greatly in creased e g myelomatosis (p 146)

Of course the presence of abnormal substances or abnormal quantities of normal substances such as bilirubin are also significant especially in haemolytic diseases

Blood serum is essentially the same as plasma except that the fibrinogen has been removed in the process of clotting

Blood Groups

There are four main groups in man and although a number of sub groups have been discovered in recent years it will be sufficient for the present purpose to outline the older knowledge The investi gation of blood groups irregular antibodies etc is so highly specialized a procedure that it must be entrusted to special labora tories

The four main blood groups depend upon the fact that the human red corpuscles may contain two agglutinable substances which are known as A and B These may both be present (blood group AB) or only one may be present (group A and group B) or neither may be present (group 0)

Human serum may also contain agglutinins which naturally do not agglutinate their own corpuscles These agglutinins are known as α and β Thus in serum of group A β is present which can agglutin ate corpuscles of group B In the serum of group B α is present while in the serum of 0 both α and β are present Obviously therefore the serum of AB contains no agglutinins

A full description therefore of the four groups would be $A = A\beta$ $B = B\alpha$ $O = 0\alpha\,\beta$ while the full description of the fourth is AB

The genes of the four blood groups are inherited according to definite laws and investigation may be of value in cases of disputed paternity The details of this are too complicated to be discussed here and are in any case not of clinical value Other factors which are not of very great significance in connexion with blood transfusion

are known as M N and P while recently other factors have been discovered None of these are however sufficiently important to find a place here the same is not true however of what is known as the rhesus system (Rh)

It is now known that erythroblastosis (haemolytic disease of the newborn p 99) depends upon an antagonism between the blood of the foetus and that of the mother This is very rarely due to the ABO system but depends upon an entirely separate one—the Rh system Very briefly it may be said that mankind is divided into two groups viz those whose blood contains the factor Rh and those from whose blood it is absent An Rh positive foetus developing in an Rh negative woman will evoke the formation of anti Rh substances This is a soluble haemolysin which is essentially the cause of the haemolytic disease of the newborn and is occasionally the cause of severe or even fatal transfusion reactions

NORMAL FIGURES

Red corpuscles	4 8–5 5 million per c mm
Haemoglobin	12–15 grammes per c c

It is still usual to give the haemoglobin figure in the form of a percentage the normal being between 90–96 per cent

Leucocytes	4–9 thousand per c mm
Platelets	200 000–350 000 per c mm

Differential count

	per cent
Neutrophils	
Staff forms (very slightly immature)	4
Polymorphs	33–70
Eosinophils	1– 5
Basophils	0– 2
Lymphocytes	15–50
Monocytes	4– 8

Plasma Proteins

Albumin	3 4–6 7
Globulins	1 2–2 9
Fibrinogen (in plasma)	0 2–0 6

The total plasma proteins i e fibrinogen albumin and globulins =5 8–8 6 per cent

Serum proteins i e albumin and globulins=5 6–8 5 per cent

the red cell once it has performed its function it disappears but it seems that on the average its duration of life is two to four days

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SECTION II

THE ANAEMIAS

Various indices

Colour index — $\dfrac{\text{Haemoglobin percentage}}{\text{red corpuscles in millions} \times 100}$

Diameter of red corpuscles — Price Jones curve
Diffraction methods
normal mean diameter = about 7 2 microns

Mean Corpuscular Haemoglobin Concentration (M C H C) = $\dfrac{\text{Haemoglobin in grammes per 100 ml blood}}{\text{Vol of packed red cells per 100 ml blood}}$

Normal is 32–38 per cent

This value represents the real concentration of haemoglobin in the blood It is therefore useful too in recognizing iron deficiency

Mean Corpuscular Volume (M C V) = $\dfrac{\text{Volume of packed cells per 1 000 ml blood}}{\text{Red cells in millions per c mm}}$

Normal is 78–94 cubic microns ($c\,\mu$)

THE ANAEMIAS

INTRODUCTION

THE term anaemia has two main meanings Thus clinically it is often loosely employed to mean nothing more than pallor which may or may not be accompanied by abnormality of the blood More accurately the term is used to mean a reduction below normal levels in the number of red corpuscles in the quantity of haemo globin or of the volume of packed red corpuscles or to two or all three of these states

Although the haematological definition of anaemia is the more accurate it must be remembered that anaemia was a condition re cognized by clinicians long before the more delicate criteria had been worked out and initially at least it is our purpose here to emphasize the symptoms and signs on which a clinical diagnosis of anaemia and of blood disorders in general can be based Even so it is essential to give an account of the modern haematological classification of anaemias

Briefly it may be said that the causes of anaemia are as follows loss of blood (*haemorrhagic anaemia*) destruction of blood in the body (*haemolytic anaemia*) failure of adequate formation of blood as a result of some deficiency (*deficiency anaemia*) and destruction of the formative organs (*hypoplastic* and *aplastic anaemias*)

Apart from such an aetiological classification although not in contradiction to it there is a more morphological one which has much to commend it particularly to the laboratory worker Thus the average size of the red corpuscles may be greater than normal (*megalocytic* and *macrocytic anaemias*) If as is usual in these con ditions there is an excess of haemoglobin one speaks of *hyper chromic megalocytic* or *macrocytic anaemia*

Megalocytic anaemia occurs when the amount of haemopoietic principle is deficient (see also p 66) and in addition to the usual symptoms and signs of anaemia this state presents certain clinical features on which a diagnosis may often be based

In contradistinction there is a state in which the average content of haemoglobin is less than normal this is *hypochromic anaemia* which is due to a deficiency of iron however brought about As a

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rule the average diameter of the corpuscles is decreased in this condition, and one then speaks of *hypochromic microcytic anaemia*. Finally, there can be reduction of haemoglobin and red corpuscles in equal proportions while the average diameter is unchanged. This is *normocytic normochromic anaemia* such as occurs as an immediate result of haemorrhage, in aplastic anaemia and in some types of haemolytic anaemia.

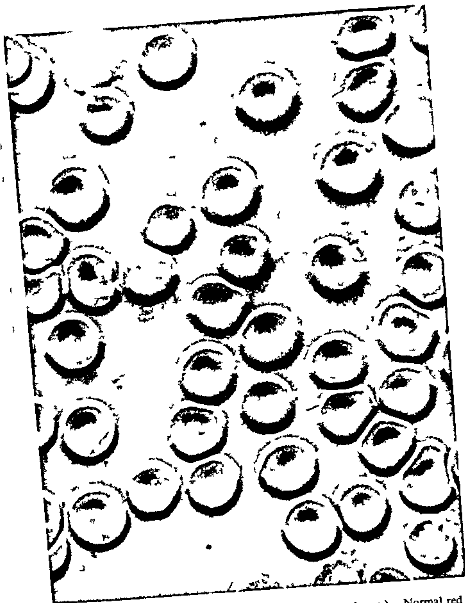


Fig 3 (*a*)—Red Corpuscles (shown by the method of ombrage) Normal red corpuscles



FIG 3 (*b*)—Red Corpuscles (shown by the method of ombrage) Pessary corpuscles in hypochromic anaemia (*by courtesy of Dr M Bessis Centre National de Transfusion Sanguine Paris*)

CHAPTER III

TYPES OF ANAEMIA

Causes of Anaemia

THROUGHOUT life there is continuous destruction of effete red corpuscles and formation of new ones During this process haemoglobin is of course liberated and is broken down into two parts the one containing the iron and the other the protein The former is split again into an iron-containing substance which is used for the formation of fresh haemoglobin while the iron free moiety is ex creted mainly as bilirubin in the bile although some goes to the formation of urobilin and stercobilin

Clearly then considerable amounts of the constituents of red corpuscles and of haemoglobin must be available if the blood picture is to be kept constant This is a fundamental fact to be borne in mind in a discussion of the causes of anaemia

Anaemia Due to Loss of Blood

Sudden loss of a large amount of blood must always cause an anaemia which is of course proportional to the amount lost while transiently the total blood volume also falls Very rapidly fluid passes from the tissues into the circulation and then of course there is reduction in the number of corpuscles per unit volume of blood while the haemoglobin is proportionately reduced The colour index is therefore the same as it was before the haemorrhage but as the total amount of the respiratory pigment is diminished there is anoxaemia of all the tissues including the bone marrow which is stimulated to increased formative activity by this reduction of oxygen tension But if the amount of blood lost has been considerable there will be a shortage of the necessary materials for the formation of new corpuscles especially of iron which is not stored in large amounts in the tissues except in inaccessible form mainly as myohaemoglobin in the muscles which is almost immune from reduction by increased demands on the part of the marrow It is obvious therefore that during the process of restitution there will be insufficient iron available and in consequence the colour index will fall i e hypochromic anaemia will develop

Repeated smaller losses of blood (*chronic haemorrhagic anaemia*) will naturally, be of the same type but the hypochromia is likely to be even more intense because of the prolonged depletion of the iron reserves of the body

A moment's thought will show that any deficiency of iron however caused will lead to hypochromic anaemia

Iron deficiency Anaemia

The anaemia that follows haemorrhage acute or chronic is to a very great extent due to reduction in the amount of iron available for the formation of haemoglobin but it is not customary to include the haemorrhagic anaemias among the iron deficiency ones perhaps because loss of blood is so spectacular an event

Iron deficiency may arise in a variety of ways viz insufficient in take inadequate absorption from the intestine and theoretically at least incomplete utilization of available iron in the tissues

Iron deficiency anaemia due to insufficient intake is a relatively common condition especially in women in the reproductive age because of the considerably monthly loss of the metal and also of the strains of repeated pregnancies It is true to say that in spite of the conservation of most of the iron from destroyed red corpuscles the average person lives rather near the verge of iron deficiency mainly because a good deal of the iron present in food is not converted into a form capable of absorption in the intestine Any cause of increased utilization of iron may therefore lead to the development of hypo chromic anaemia For instance during pregnancy especially during the last three months or in cases of twins the demands of the foetus may be so great as to deplete the maternal tissues of iron

Iron deficiency anaemia due to inadequate absorption is a very common condition which occurs most strikingly if there is absence or gross deficiency of hydrochloric acid in the gastric juice This is perhaps the commonest cause of chronic hypochromic anaemia in middle aged women but it also occurs after extensive resection of the stomach and less commonly as a result of gastric cancer In fact in the absence of hydrochloric acid only about half as much iron as normal is absorbed

Another cause of deficient absorption of iron is as might be expected chronic diarrhoea whatever its cause For example in sprue hypochromic anaemia is the rule and it is only in the most severe or the very prolonged cases that the anaemia becomes of the pernicious type

Anaemia due to incomplete utili ation of iron is not a clearly defined

condition but there is no doubt that the metabolism of iron is dis turbed in many infections and the associated anaemia is almost certainly due to failure to use the substance On the other hand this is not a complete explanation because in some cases of anaemia associated with infection intravenous injection of iron is about thirty times as effective as is a similar dose by mouth indicating that failure of absorption is at least as important as inability to metabolize the metal

Anaemia due to deficiency of a specific haemopoietic substance As is now well known in 1925 Minot and Murphy published their results on the treatment of pernicious anaemia by a diet containing large amounts of uncooked liver This was the beginning of the modern treatment of this disease which is now known to be due to absence or deficiency of a specific substance in the liver

It was not long after this first publication that liver extracts for oral administration were prepared and proved to be quite efficacious Then rather crude extracts containing a considerable amount of protein suitable for intramuscular injection were prepared and found to produce almost dramatic response in every case of true pernicious anaemia From such extracts a substance known as fraction G which contained neither protein nor fat was obtained and it was found that 10 grammes of this preparation given by mouth were quite as effective as 400 grammes of whole liver while half a gramme injected had the same effect Further purifications were carried out until extremely active extracts became available although the nature of the essential principle was still unknown

It was found however that administration of an efficacious extract was rapidly followed by an increase in the number of reticulocytes and secondly by a continuous and steady rise in the number of red cells and haemoglobin While these changes were occurring megaloblasts very quickly disappeared from the marrow and were replaced by normoblasts In this way a complete remission with a normal blood picture and a normal marrow could be produced and main tained as long as the treatment was continued

Folic acid was then discovered and was found to have a similar effect on the megaloblasts in the marrow in cases of pernicious anaemia and for a short time it was supposed that this was the essential haemopoietic substance This has been disproved and folic acid is now of very limited therapeutic value

The most recent step has been the isolation of a cobalt-containing substance now known as vitamin B 12 As small an amount as 10 microgrammes of this will take the place of an ordinary dose of

liver extract and continued injection of vitamin B 12 will produce and maintain a remission

It may thus be said that some substance probably vitamin B 12 present in the liver in health is essential for the normal maturation of red corpuscles and that in its absence erythropoiesis becomes megaloblastic instead of normoblastic as in health

Further discussion of this subject together with details of treatment of pernicious anaemia will be found on page 68 and of other macrocytic anaemias on p 5

Haemolytic Anaemias

Anaemia due increased destruction of blood Normally throughout life the older red corpuscles are continuously being destroyed in the reticulo endothelial system particularly in the spleen while there is an equal production of new ones in the bone marrow The exact mechanism by which the effete corpuscles are removed is still uncertain but it is probably partly humoral i e due to some substance or some physico chemical change in the spleen capable of destroying red corpuscles or at least of preparing them for destruction by phagocytes

Clearly then excessive destruction of red corpuscles if not completely compensated by an equal increase of formation will lead to anaemia

There are obviously three main possibilities in the aetiology of haemolytic anaemia viz increased destruction due to abnormalities of the red corpuscles or to the presence of haemolytic substances in the plasma or to increased phagocytic activity in the reticulo-endothelium.

Haemolytic anaemia associated with abnormalities of the red corpuscles The best known example of this type of haemolytic anaemia is *acholuric family jaundice* a condition in which the red corpuscles *in vitro* present a reduced resistance to the action of hypotonic saline This increased fragility is accompanied by an abnormality of shape the corpuscles being spherical (*spherocytes*) instead of discoid (p 86)

Another example of haemolysis due to some abnormality of the corpuscles is *nocturnal haemoglobinuria* (p 95) Here the red corpuscles appear normal in structure while they are also normal in their behaviour in hypotonic saline Although no abnormal haemolytic substances are demonstrable in the blood plasma the corpuscles undergo destruction in the circulation possibly mainly in the spleen and other parts of the reticulo-endothelial system Not

only are the corpuscles in this disease destroyed by the patient s own blood plasma but also by any normal plasma and a possible ex planation is that their abnormality is a diminished resistance to complement

Structural abnormalities of the red corpuscles do not always or continuously lead to increased destruction For instance in *sickle cell anaemia* (p 88) the intensity of haemolysis varies from time to time although the peculiarity of the red corpuscles is persistent

Sometimes an increased liability to destruction is due to infection and the most striking example of this is of course malaria Here the intra-corpuscular position of the parasite leads to destruc tion but in some cases there are in addition haemolysins in the circulation (blackwater fever)

Haemolytic anaemia due to haemolysins A haemolysin is a sub stance which can destroy red copuscles It may act in a relatively simple and direct manner as in the case of phenyl hydrazine which on account of this action is used in the treatment of polycythaemia vera (p 150) Similarly the venom of some snakes destroys red corpuscles by a direct action perhaps on their lipoid surface layer

The term *haemolysin* is however usually reserved for substances of the nature of immune bodies which require the presence of com plement for their action

In many cases of *acquired haemolytic jaundice* the blood contains substances capable of destroying the patient s own corpuscles or at any rate of coating them so that they are more liable to destruc tion (see p 104) A striking example of such a condition to which a great deal of attention has been directed recently is the *haemolytic disease of the new born* (p 101)

Very briefly this malady is brought about in the following manner

If a woman whose blood does not contain the Rhesus factor (i e who is Rh negative) bears a foetus that does contain this factor (i e which is Rh positive) she will develop antibodies (anti Rh) which can act upon and destroy Rh positive corpuscles As a rule the con centration of anti Rh during a first pregnancy does not rise high enough to cause damage to the foetus but after several Rh positive pregnancies an Rh negative woman may develop so much of this substance that the baby is born with or develops the haemolytic disease of the new born (p 101)

An identical condition can result if an Rh negative woman has received transfusion or intramuscular injections of Rh positive blood *Then owing to the presence of preformed anti Rh in the* woman s blood even a first Rh positive foetus may be so damaged as

to develop haemolytic disease Furthermore if such a woman received further transfusions of Rh positive blood severe (and perhaps fatal) haemolysis would ensue Clearly then, it is of the utmost importance never to infuse Rh positive blood into an Rh negative woman especially during the reproductive age *Indeed Rh positive blood should never be given to Rh negative people*

Finally haemolytic anaemia can result from infection by such bacteria as haemolytic streptococci but here there is an additional factor in the genesis of the anaemia viz marrow damage which interferes with adequate regeneration of red corpuscles a hypoplastic condition

It is of the utmost importance to realize that chronic haemolysis can be present even in the absence of anaemia because if the marrow is healthy it will be able to supply an adequate number of red corpuscles many of which although immature are functionally efficient It is therefore characteristic of the blood in chronic haemolytic conditions whether accompanied by anaemia or not to find large numbers of immature corpuscles (reticulocytes) If these are sufficiently numerous to keep the total number of corpuscles in the circulation up to normal numbers one might consider the state as being one of compensated anaemia even so symptoms due to the haemolytic condition (e g jaundice etc) may be present

Hypoplastic and Aplastic Anaemias

The maintenance of a normal state of the blood depends upon the functional integrity of the blood forming organs of which in post natal life the bone marrow is the most important Any damage to that tissue is therefore very likely to lead to anaemia because of failure to replace the normal wastage of corpuscles

Aplastic anaemia can result from a great variety of causes Thus certain poisons of which benzol is a striking example can cause almost complete destruction of marrow tissue with consequent aplastic anaemia (p 109) Similarly gross decrease in the size of the medullary cavities e g due to osteosclerosis or to widespread metastases of tumours can lead to a rather similar condition (see leuco erythroblastic anaemias p 116)

CHAPTER IV

ANAEMIA DUE TO LOSS OF BLOOD

THE causes of *acute post haemorrhagic anaemia* are very numerous and belong mainly to the field of general surgery and medicine

Symptoms

The clinical picture will differ somewhat according to the nature of the underlying disorder but the symptoms due to sudden loss of blood are essentially the same whatever the cause The size of the haemorrhage its rapidity and to a less extent its site will affect the picture For example a very slow but severe loss of blood may result in the loss of 50 per cent of the total volume without death ensuing whereas the loss of 33 to 25 per cent occurring rapidly would be fatal

The characteristic signs of acute loss of blood are prostration restlessness thirst sweating rapid thready pulse low blood pressure and rapid shallow breathing Of these rapid pulse and low blood pressure have long been regarded as the most significant signs but in point of fact they are liable to be misleading because they may not become manifest sufficiently early if the patient is young and healthy and is recumbent during the time bleeding occurs This is particularly well shown when 500 c c of blood are removed from a blood donor in whom there will be no symptoms at rest while the pulse rate and blood pressure remain within normal limits If however he rises quickly immediately after the blood letting the pulse rate increases slightly and there may be dyspnoea and sometimes faintness all of which are of course quite transient

Not even blood examination will always give an indication of the severity of haemorrhage because vaso constriction can produce a misleadingly high count while dilution of the blood by passage of tissue fluids into the circulation can produce an apparently low one

Bleeding into the intestinal tract if at all severe is accompanied by a rise in the level of blood urea and this is within limits a useful index to the amount of blood that has been lost If the level rises to 150 mg per 100 c c or higher the outlook is grave

Bleeding into a body cavity e g the pleura or peritoneum is often followed by slight jaundice due to breakdown of haemo globin

Moderate pyrexia may accompany gastro-intestinal haemorrhage and almost invariably does so if bleeding occurs into the substance of any organ including the muscles

Blood Picture

The earliest change is of course, a fall of red corpuscles This is soon followed by an increase of blood platelets accompanied by a decrease in the coagulation time This occurs within an hour or less while at the same time leucocytosis develops In other words there is an immediate indication of increased marrow activity although immature red corpuscles (reticulocytes) do not increase until twenty four or thirty six hours later reaching their maximum towards the end of the first week

Immediately after the haemorrhage the colour index remains the same as before it occurred but when regeneration becomes active the colour index tends to fall because the efficiency of the marrow in producing the stroma of red corpuscles is greater than that in synthesizing haemoglobin

Ten to fourteen days after the haemorrhage there are as a rule no signs in the peripheral blood of active red cell regeneration while the leucocyte and platelet counts will have returned to normal within three or four days

If the reticulocytes remain high it is probable that bleeding is still continuing If the colour index is found to be low during or immediately after the haemorrhage it is probable that there have been previous losses of blood

Treatment

Discussion of treatment of the emergency does not form part of our present purpose it follows routine lines but the question of subsequent adjuvant treatment is important Thus a diet rich in protein vitamins and minerals is obviously essential in order that the body shall have available all the substances needed for blood regeneration There is no indication for the use of liver extract by injection and its only value if given by mouth lies in its high con tent of nutritive substances

As a rule administration of iron is unnecessary because in the majority of people the storage depots contain a sufficient amount On the other hand iron can do no harm and if there is a deficiency

it will do good in shortening the time needed for recovery of the original haemoglobin level

Simple Chronic Anaemia

Although this rather ill defined state is not necessarily due to persistent loss of blood it falls to be discussed in this section because among its many causes chronic haemorrhage is one This is the condition often known as secondary anaemia but this is an unsatis factory term and should be given up

Blood Changes

In general it may be said that anaemia of this type is rarely very severe and that the colour index is little if at all reduced

Slight signs of blood regeneration anisocytosis with some poikilocytosis are almost invariable but polychromatic corpuscles and nucleated red cells are not commonly seen

Reticulocytes are not as a rule increased

The leucocyte picture depends upon the nature of the causative disease

The state of the blood of course depends upon that of the bone marrow Marrow puncture has proved that as a rule there is how ever little or no hypoplasia of the marrow and indeed there may be increase of white cells and of the less mature forms of red cells

Causation

(a) *Inflammatory diseases* especially chronic ones are usually accompanied by a simple chronic anaemia This is striking for example in rheumatoid arthritis osteomyelitis etc

Moderate anaemia is usual in rheumatic fever but varies in in tensity with relapses and remissions

Mild anaemia is common in tuberculosis but the presence of severe anaemia should immediately arouse suspicion of some com plication for example superadded infection or intestinal stricture

In sub-acute bacterial endocarditis mild anaemia occurs in most cases while in a few it is very severe In this type signs of active blood regeneration are often more marked than in the other infective types

(b) *Kidney diseases* The anaemia that may occur in association with renal disease varies more or less proportionately with the degree of nitrogen retention It may therefore become severe when the blood urea is very high

(c) *Malignant diseases* Cancer does not necessarily cause anaemia

but, if there is interference with nutrition, simple chronic anaemia may develop and become severe If however, persistent loss of blood occurs hypochromic anaemia will develop If there are wide spread secondary deposits in the bones a leuco-erythroblastic anaemia may ensue or even a myelophthisic one may manifest itself

(*d*) *Liver disorders* Any type of anaemia may occur in association with hepatic disease but as a rule in cirrhosis the anaemia is of the simple chronic type Other varieties are discussed on page 80

(*e*) *Nutritional* Faulty absorption as in cases of chronic dysent ery may produce a simple chronic anaemia but it is surprising how long the disease may persist without any signs of anaemia

(*f*) *Infestation by parasites* Most parasites do not cause anaemia unless their presence causes defective nutrition or loss of blood In rare cases the anaemia may be due to some substance secreted by the parasite For example hook worm infestation produces anaemia which may be very severe as the result of chronic loss of blood The fish tapeworm is a cause of an anaemia haematologically indis tinguishable from pernicious anaemia although it occurs only in a small proportion of the infested persons (p 80)

(*g*) *Endocrine disorders* It is surprising how few are the blood changes associated with disorder of any internal secretion A mild and simple chronic anaemia may occur in association with hypothy roidism or with pituitary insufficiency but this is not a characteristic feature and may often be absent

(*h*) *Vitamins* Apart from vitamin B 12 (p 70) none of the known vitamins *directly* affect blood formation

(*i*) *Pregnancy* Mild simple chronic anaemia is commonly found in normal pregnancy reaching its maximum about the twenty fifth to thirtieth week

Treatment

In all such cases administration of iron may be useful but clearly the essential step is the treatment of the underlying causative condi tion

The subjects of iron metabolism and of iron as a haematinic are dealt with on page 56

Anaemia as well as other symptomatic blood changes is dis cussed in Chapter XX

CHAPTER V

IRON DEFICIENCY ANAEMIAS

THE great majority of anaemias fall into this group although their aetiology varies widely

One of the simplest examples is *anaemia due to chronic haemorrhage* This forms part of the picture of many cases of haemorrhoids chronic gastric ulcer and indeed any condition in which blood is lost at intervals over long periods of time

The clinical features are usually overshadowed by the symptoms of the underlying disease but in many cases much symptomatic improvement can be obtained by dealing with the anaemia

The features of the anaemia itself are those of anaemia in general (see Chapter I) but in addition the pallor often presents a peculiar yellowish grey tinge which could be mistaken for a slight degree of jaundice It differs however inasmuch as the sclera is not yellow and blood examination does not reveal in increased icterus index or a positive Van den Bergh reaction

The blood picture in these cases is pathognomonic of an iron deficiency anaemia with adequate regeneration of the blood but it does not of course indicate the site of the bleeding

The reduction in the number of red corpuscles is distinctly less than that of the haemoglobin and the colour index is therefore reduced often being in the region of 0 7 or 0 6 The number of leucocytes does not differ much from normal but the percentage of neutrophils is often low the lymphocytes being increased relatively or occasionally absolutely

In films some of the red corpuscles show slight increase in the size of the area of central pallor although a few may even present a pessary appearance There is moderate anisocytosis but the average diameter of the red corpuscles is normal or more commonly slightly reduced In short then the anaemia is of the hypochromic normocytic or more commonly of the hypochromic microcytic variety

Slight abnormalities of shape are quite commonly seen in some of the red corpuscles and it must be realized that such poikilocytosis is not as is sometimes thought pathognomonic of pernicious anaemia

It must be admitted however that extreme degrees of poikilocytosis are very suggestive of that disease

Polychromasia is always present but slight This is of course another sign of active blood regeneration because polychromatic corpuscles are slightly immature In vitally stained films, the per centage of reticulocytes is slightly higher than normal and this forms an excellent index of the intensity of regeneration Reticulocytes are slightly immature red corpuscles which are set free from the marrow in conditions of reaction to increased demand They are more easily recognized than are polychromatic corpuscles but they are really the same elements demonstrated by a different method

If the anaemia is severe a few normoblasts with extremely dense nuclei may be found in the peripheral blood but this is not common in uncomplicated cases

A few corpuscles containing basophilic granules (punctate basophilia or stippling) may be found in cases of chronic post haemorr hagic anaemia but these are not common except for some unknown reason if bleeding has occurred into the gastro intestinal tract Even then the number of stippled corpuscles is never large

The leucocyte picture with its relative or even absolute lympho cytosis seems to be the result of depression of myeloid activity in the marrow almost suggesting that a marrow actively engaged in the production of red corpuscles is unable to produce a normal number of granulocytes

Platelets are usually at the higher limits of normal but in some cases are considerably increased This probably plays a part in causing the thromboses which are not an uncommon complication of chronic anaemia of this type

Marrow puncture reveals a very cellular marrow with a relative increase in the cells of the erythropoietic series particularly of baso philic and polychromatic normoblasts There is also increase in the percentage of immature granulocytes mainly of the myelocytes There is thus no real defect of granulopoiesis but some interference with maturation It may well be that such maturation defect is due to some nutritive factor or factors which are normally used for the production of granulocytes being diverted to the nutrition of the actively proliferating red cell series

Treatment

Clearly the essential step in treatment is the cure of the under lying causative condition but symptomatic relief can be obtained by administering iron by mouth This is best given in the form of ferrous

sulphate of which about thirty grains a day are necessary In cases of gastro-intestinal haemorrhage it may be necessary to give the iron parenterally in order to avoid irritation of the stomach

The amount of iron that can be given intramuscularly is so small *as to be valueless and if iron is to be given parenterally it must be* given intravenously A number of suitable preparations are now commercially available but all require to be given with considerable care because of the possibility of producing local thrombosis If the injection is made slowly the likelihood of thrombosis is greatly decreased but it is undoubtedly better to give intravenous injections of iron in a more complicated way viz by running normal saline into a vein through a funnel and tube and then injecting the preparation of iron through the rubber tube so that it is diluted and washed well into the vein If this is done thrombosis never ensues This method is also useful for the intravenous injection of other irritant substances e g nitrogen mustard (p 160)

If an adequate amount of iron is given a reticulocyte increase will occur five to eight days after starting treatment This is of course an indication that the response of the marrow is adequate but unless the bleeding is stopped the marrow may well fail to raise the red corpuscles and haemoglobin to normal levels

If the bleeding has been stopped before iron is given one finds that the reticulocyte increase is much greater than in those cases in which bleeding is still continuing

There is a relationship between the level of haemoglobin and the height of the reticulocyte crisis that follows the administration of iron The lower the *initial level of haemoglobin* the greater the height of the reticulocyte increase This is particularly interesting because in pernicious anaemia there is a relationship between the reticulocyte increase that follows injection of liver and the *initial level of the red corpuscles* Presumably the explanation is that in the former iron is needed for the formation of haemoglobin whereas in the latter haemopoietic factor is needed in the production of the stroma of red corpuscles

Chlorosis

This is a particularly striking example of iron deficiency anaemia which for some unknown reason has become extremely uncommon The disease has been recognized for some 400 years perhaps because of the striking greenish pallor which is the origin of the name

The disease occurred in adolescent girls and was rarely seen after the age of twenty five

The clinical features apart from the greenish pallor were those of any other anaemia but palpitation was one of the commonest symptoms while amenorrhoea was also common The disease ran a benign course and responded rapidly and completely to treatment The only complication which was at all common was thrombosis usually of a femoral vein

The decrease in frequency remains unexplained but is perhaps due in part to improved diagnosis which has enabled us to distinguish the anaemias due to tuberculosis, etc It must however be realized that a mild hypochromic anaemia without the typical greenish pallor of the skin is still quite common in adolescent girls

Blood Picture

A striking feature was the reduction in the amount of haemoglobin greatly out of proportion to the decrease in the number of red corpuscles Indeed the latter might be normal while the colour index was as low as 0 4 The number of leucocytes was normal the platelets were often moderately increased

Treatment

The only treatment required is administration of iron in adequate doses The correction of digestive disturbances and constipation are useful adjuvants but the only essential is the administration of iron

Chronic Hypochromic Anaemia

This is a common disorder especially in middle aged women although no age or either sex is exempt It presents the general features of chlorosis but is accompanied or predisposed to by achlorhydria

Although the condition is distinct clinically and haematologically from pernicious anaemia there are some resemblances Thus its incidence is commonest in persons of the same physical type as those who develop pernicious anaemia viz persons of blond hair and complexion with the eyes set rather widely apart and with a tendency to premature greying of the hair

The importance of a constitutional factor is also shown by the frequency with which a family history of anaemia is found in these patients Occasionally families have been observed in which one or more members male or female have had pernicious anaemia while hypochromic anaemia has occurred in others mainly of course in the women

The geographical distribution of the disease is not quite the same

as that of pernicious anaemia Thus both diseases are common in the Scandinavian countries and indeed in the whole of northern Europe and North America But in Italy South America and China pernicious anaemia is relatively rare while chronic hypo chromic anaemia is common In short then the constitutional factor in the development of hypochromic anaemia is less well marked than in the case of pernicious anaemia

Symptoms

The onset is extremely insidious and the progress gradual pre sumably because the stores of iron in the tissues are only slowly exhausted Symptoms at first slight may develop so slowly that as much as a quarter of a century separates the first onset from the time that the patient seeks advice It is quite common to elicit the in formation that the patient has never quite picked up from her last pregnancy The extremely slow progress of the disease permits of adjustments in the tissues and for this reason an extreme degree of anaemia may be present while the patient complains of nothing worse than tiredness There is no doubt that many of these patients are diagnosed as suffering from a neurosis when in fact their symp- toms physical and mental are due to deficient oxygenation of the tissues

Gastro intestinal disturbances such as capricious appetite epigastric discomfort after meals and constipation with alternating diarrhoea are relatively common These are in part doubtless due to the poverty of the blood supplied to the gastro-intestinal tract but the major factor in the development of these symptoms is achlor hydria This is not as invariable as in cases of pernicious anaemia but it occurs in over 80 per cent of the cases

X ray examination of the gastro intestinal tract does not reveal the presence of any gross abnormality in the majority of cases It is however interesting to find that hernia through the oesophageal hiatus of the diaphragm is often associated with chronic hypochromic anaemia Such a *hiatus hernia* is much more commonly seen in women than in men but the explanation of the chronic hypochromic anaemia that may accompany it is obscure Certainly it is not com mon to find achlorhydria in such cases and possibly anaemia associated with diaphragmatic hernia should be placed in a separate group in which the cause of the deficient absorption of iron is different although the blood picture and the symptoms are the same Whether this be the case or no it should be emphasized that cases of persistent hypochromic anaemia which do not respond adequately

to administration of iron should, therefore be investigated to exclude the possibility of such hernia Often there are no clinical symptoms suggestive of the hernia but occasionally there is discomfort after meals which is greatly aggravated by lying down and which is immediately relieved by vomiting. If such symptoms are present the oesophagus and stomach should be X rayed (Fig 2a and 2b)

Soreness of the tongue or mouth is not as common as in pernicious anaemia and its severity is also less Even so after many years of chronic anaemia some degree of atrophy of the papillae of the tongue is found This is not as evenly distributed as in pernicious anaemia and one often finds that denudation of the papillae is patchy

Whether independently of the glossitis or associated with it there may be difficulty in swallowing or spasm in the throat while attempting to swallow This is so striking in some cases (and may indeed be the presenting symptom) that it has been called the *Plummer Vinson syndrome* As a rule the patient complains of pain or burning sensation as food passes behind the larynx or less commonly she says that it feels as if the food sticks at this point

It is important to realize that the Plummer Vinson syndrome may occur and persist for many months or years even when there is in the ordinary sense little or no anaemia These cases can only be recognized with certainty by estimation of the level of the plasma iron It appears that the dysphagia of the Plummer Vinson syndrome is not directly associated with reduction in the amount of haemoglobin or in the number of red corpuscles but with the decrease in the level of iron in the plasma For this reason it has been suggested that this syndrome should be known as *sideropenic dysphagia*

Administration of large doses of iron by mouth even in the absence of anaemia will to some extent relieve the difficulty in swallowing but such relief is rarely complete This is particularly so in the advanced cases in which the lining of the upper oesophagus has undergone organic changes

It is of course well known that post cricoid carcinoma is commoner in women than in men, and there is no doubt that the Plummer Vinson syndrome predisposes to its development This is apparently true even when the anaemia has been relieved by administration of adequate amounts of iron

Heart

Tachycardia and arrhythmia are particularly common in chronic hypochromic anaemia even when it is not very severe If these are accompanied by oedema of the ankles and puffiness of the face

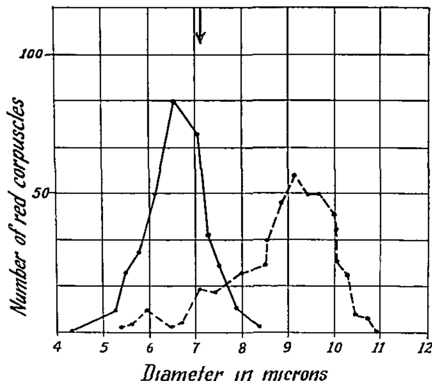


FIG 4 —Price Jones Curve The left hand curve is from a microcytic anaemia the right hand curve from a macrocytic anaemia The arrow indicates the normal average diameter of red corpuscles (The curve is taken from a laboratory note book and is not smoothed)

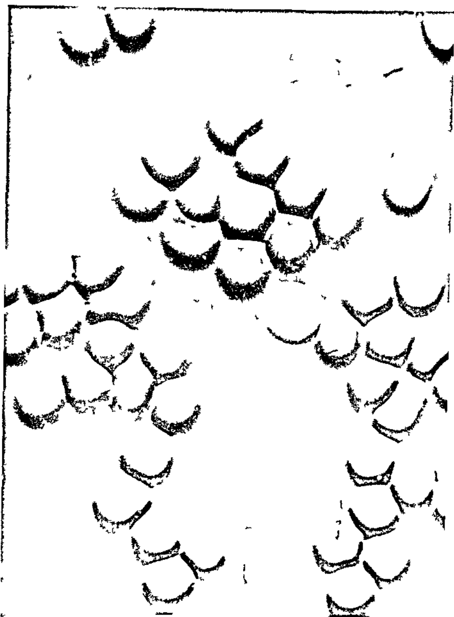


FIG 5 —Spherocytes (shown by the method of ombrage) The absence of central depression is obvious (*by courtesy of Dr M Bessis Centre National de Transfusion Sanguine Paris*)

which are quite common there is a distinct resemblance to chronic nephritis and congestive cardiac failure

Indeed in severe cases of anaemia the latter condition may occur as a complication which it is important to recognize because it urgently requires treatment This is one of the conditions in which intravenous injections of iron are specially useful Of course digitalis may also be needed

In the *genito-urinary system* the disturbance of the menstrual cycle is common Amenorrhoea is usual in the more severe cases but menorrhagia is not very uncommon It must be emphasized that excessive menstrual loss may cause anaemia but that such excessive loss is sometimes a sign of an established anaemia particularly of the chronic hypochromic variety

The symptoms referable to the urinary tract are not severe but complaints of polyuria with the passage of large quantities of very pale urine are quite common No abnormal substances are found in the urine and the blood urea is within normal limits

The *endocrine system* appears to be more or less normal in cases of chronic hypochromic anaemia although signs of slight degrees of hypothyroidism can often be detected These are certainly not due to the anaemia and do not improve when it is cured Whether hypothyroidism plays a part in the genesis of chronic hypochromic anaemia is also uncertain but there is no doubt that treatment of the hypothyroidism at the same time as administration of iron is followed by more rapid haematological response

Nervous System

There are no characteristic neurological symptoms associated with chronic hypochromic anaemia and organic disease of the central nervous system such as is common in pernicious anaemia never develops Non specific neurological troubles such as numbness and tingling especially in the legs are frequent if the anaemia is at all severe but they disappear rapidly as the anaemia is relieved

The Skin

Even if there is no striking loss of subcutaneous fat the skin often appears unduly wrinkled and the normal elasticity is diminished

The hair tends to go grey early and although the individual hairs tend to become coarse they are shed in excessive numbers

Other cutaneous structures also show signs of malnutrition One of the most striking being the development of concave nails (spoon nails) which are extremely brittle and may be tender This condition

is often preceded by the development of longitudinal ridging of the nails In adequately treated cases the nails become normal as they grow out As in the case of the Plummer Vinson syndrome this condition of the nails does not appear to be directly due to the anaemia but is associated with the low level of plasma iron

The Spleen

The lower pole is occasionally palpable but gross enlargement never occurs

Menorrhagia is commoner than is diminished menstrual loss It is important to realize this because severe anaemia in menopausal women is often attributed to flooding when in fact the anaemia is the cause of the greatly increased menstrual loss Then again there is a much greater tendency to menorrhagia at the menopause in patients suffering from this type of iron deficiency anaemia

Slight functional nervous disturbances may occur such as pins and needles but no syndrome similar to sub acute combined degeneration of the spinal cord ever manifests itself

Blood

The blood picture in a fully developed case is that of hypochromic microcytic anaemia There is marked reduction in the amount of haemoglobin while the red cell count is surprisingly high It may indeed even be normal Most commonly however the red cell count is in the region of 4 000 000 per c mm while the haemoglobin is about 50–60 per cent

In films many of the red corpuscles are seen to be poorly filled with haemoglobin some indeed have only a narrow stainable rim (pessary corpuscles) The average diameter of the red corpuscles is considerably decreased and may be as low as 6 2 microns (Fig 3 a and *b*)

The leucocyte picture shows no striking variations and platelets are usually within normal limits There are no signs of haemolysis the Van den Bergh reaction is negative and the icterus index is below normal

The *bone marrow* presents the appearance of a simple normoblastic hyperplasia with a considerable number of nucleated cells showing deficiency of haemoglobin

In the very early stages of iron deficiency the blood picture is very different as there is a well marked microcytosis accompanied by a slight compensatory erythrocytosis That is to say the mean diameter of the red corpuscles is less than normal but the number of corpuscles per c mm is increased If the condition is recognized at this stage

treatment rapidly effects a cure It is however not common to see cases or at least to recognize them in this early phase because the clinical symptoms are so slight The characteristic glazed red tongue is however present at this stage and indicates the need for blood examination

Treatment

In mild cases it is possible that an improvement in the quality of the diet will suffice to restore the blood to normal but as a general rule a higher iron content is essential The most common and most satisfactory preparation is ferrous sulphate given by mouth in doses up to two grammes a day Occasionally when the iron stores are very greatly depleted or when there is a great hurry in restoring the blood picture to normal saccharated iron can be given by intravenous injection (p 50)

Efficacious treatment with iron is followed by a reticulocyte increase of the same type as that which follows the commencement of liver treatment in pernicious anaemia the lower the haemoglobin the greater the reticulocyte response This is followed by a rapid increase in the amount of haemoglobin and gradual restoration to a normal blood picture In the great majority of these cases it is necessary to continue to administer iron throughout life although after the menopause the amount required is usually less than before Indeed in a few cases iron can be stopped after the menopause

Note on the Absorption and Metabolism of Iron

It was long supposed that there is a balance between absorption of iron from the stomach and small intestine on the one hand and excretion by the colon That this is untrue is shown by the fact that healthy people excrete as much iron in the faeces as they are given by mouth whereas iron given intravenously is completely retained Obviously then there must be some mechanism for the regulation of iron absorption and the experimental use of radio active (tagged) iron has confirmed this view which has some important therapeutic implications

The amount of iron lost by the average normal male is only about 1 mg daily and only the amount necessary for replacement is absorbed from the stomach and small intestine Even in iron deficiency anaemias the mechanism is not upset and absorption although greatly increased does not exceed the amount needed for haemopoiesis But the amount absorbed is not directly dependent on the haemoglobin level but on physiological or pathological needs Thus

in pregnant women whether anaemic or not absorption is greatly increased presumably as a result of the demands of the foetus Nor is the rate of absorption directly dependent upon the amount of iron in the plasma absorption from the stomach and small gut is not appreciably modified by intravenous injection of iron Obviously there must be some selective mechanism in the cells of the relevant parts of the gastro intestinal tract It is therefore assumed on very good evidence that there exists a receptor for iron which can attach iron from the gut and part with it to the plasma

The receptor is known as apoferritin it can combine with iron to form ferritin which is the essential step in the absorption of iron

So much for the more theoretical aspects of iron metabolism some more directly practical information will now be given

Response to administration of iron in iron deficiency anaemias depends at least to some extent on the amount of iron given there is as it were a threshold below which treatment is almost ineffective This is of course only an argument in favour of giving *enough* iron not for giving gross excess

Secondly most perhaps all iron is absorbed as ferrous ions although the plasma iron is probably in the form of a ferric hydroxide complex

Thirdly the iron stores of the body are normally adequate for the maintenance of a normal blood picture and indeed, are sufficient to meet very considerably increased demands e g about a third of the total red corpuscles can be lost by bleeding and yet the haemo globin level will return to normal without administration of iron

The condition in which these reserves are held is still uncertain but there is no doubt that haemosiderin which is deposited in such large amounts in haemolytic anaemias is not the normal form being in fact almost inaccessible for further synthesis of haemo globin

The anaemias in general are discussed in various chapters but here it is necessary to mention those anaemias that occur in association with many infections in which there is neither haemolysis nor loss of blood There is little doubt that in these cases there is disturbance of iron metabolism and certainly the plasma iron is always low Even iron given intravenously soon disappears What becomes of the iron is unknown it is to a great extent diverted to the infected tissues but whether this is part of the defence mechanism is question able What is clear is that anaemia of this type will not be cured by administration of iron until the causative infection is dealt with

Recovery from severe anaemia may utilize 2 g of iron a variable

amount of which can be taken from the body s reserves At the one extreme in iron deficiency anaemia all the iron must be absorbed at the other in pernicious anaemia the iron reserves are theoretically adequate to raise the haemoglobin to normal although in practice the whole reserves are apparently not always available (Hynes) *

* Hynes M *J Clin Path* 1947–8 Vol 1 pp 57–67

CHAPTER VI

ANAEMIAS DUE TO DEFICIENCY OF A SPECIFIC HAEMOPOIETIC SUBSTANCE

THE anaemias in this group have two haematological characters in common viz a greater decrease in the number of red corpuscles than in the haemoglobin so that the colour index is above 1 0 and a predominantly megaloblastic type of blood formation in the marrow

The typical disease in this group is pernicious anaemia but a number of conditions other than true Addisonian anaemia are characterized by this type of blood formation

It will be most convenient to describe the course of **true pernicious anaemia** before discussing the causation of megaloblastic anaemias in general

This disease which is much commoner in the blond races than in those of Mediterranean or Asiatic stock usually manifests itself about middle age Occasionally the onset is about the age of thirty such earlier onset being commoner when familial incidence in previous generations has been pronounced The first attack may occur in the elderly but then before making the diagnosis of pernicious anaemia it is essential to exclude all the other causes of macrocytic and megalocytic anaemia

Symptoms

Pallor often with a slightly yellowish tinge is usually the first sign to be noticed by the patient or his friends but as the reduction in the amount of haemoglobin is less than that in the number of red corpuscles anaemia may be quite severe before it becomes at all striking Occasionally pallor is to some extent masked by pigmentation of the face and hands This is most commonly patchy but if it is diffuse it may give an impression as of health

The skin does not present the transparent appearance found in hypochromic anaemias and tends to feel thickened The face and the body often present a slightly bloated appearance and it is rare to find any appreciable loss of weight Slight oedema of the ankles is usual in the more severe cases

The physical habitus (the constitutional type) in which pernicious anaemia seems to be commonest is described on page 4

Cutaneous haemorrhages are not common except in the terminal stages of untreated cases and even then are only small

A feeling of extreme weakness to which Addison himself called attention is the commonest presenting symptom Not only does this weakness affect the muscular system but also the psychical and sexual functions Occasionally the initial complaints are of giddiness headache palpitations or tinnitus

The Heart

Symptoms referable to the heart are common but signs of organic disease are unusual Thus palpitation and dyspnoea are often extremely troublesome while if the anaemia is severe precordial pain on exertion may closely simulate angina This pain is not entirely the result of the anaemia but is in fact due to the presence of atheroma of the coronary arteries which itself diminishes the amount of blood supplied to the myocordium so that the poor quality of the blood supplied will precipitate an anginal attack even if the anaemia is only moderate

Cardiac murmurs are even commoner than in other anaemias of equal severity These are as a rule systolic and are best heard at the cardiac base It is however rare to find a diastolic murmur and if one is found it will inevitably arouse a suspicion of organic cardiac disease

A venous bruit heard over the veins of the neck is only indicative of severe anaemia and is not pathognomonic of the pernicious type

Radiographically the heart is often considerably enlarged but this may well be associated with the age of these patients which is usually over forty five Slight electro-cardiographic changes perhaps attributable to the anaemia have often been described

Functional cardiac symptoms are much improved or indeed abolished by adequate treatment

Slight rises in temperature are common in untreated cases These are not due to intercurrent infection as is shown by the fact that they disappear with adequate treatment of the anaemia

Urine is excreted in relatively large amounts presumably associated with the slight generalized oedema

The Digestive System

The tongue presents changes in all cases of Addisonian anaemia At first the epithelium presents red shiny patches occasionally

associated with small haemorrhagic vesicles At this stage there may be considerable pain especially if vesicles are present The absence of complaints of pain is no excuse for not examining the tongue in suspected cases because for some unknown reason the lingual changes may be quite severe without any subjective symptoms

As time goes by it may be weeks months or even a year or two the stage of lingual atrophy supervenes At first, the edges and tip of the tongue become smooth while later the dorsum is equally affected so that ultimately the tongue is absolutely smooth and devoid of papillae Occasionally small sub epithelial varicosities are seen at the edges In cases of very slow onset in which treatment is not commenced for a very long time the musculature of the tongue may undergo a certain amount of atrophy so that the organ is small and strikingly pointed

Much less commonly the buccal and gingival mucous membranes undergo a similar but less severe atrophy Similar atrophy of the nasal and oesophageal mucous membranes has been described

Gastric Symptoms

The appetite is usually poor but quite frequently the patient states that he has taken a dislike to meat and fat but apart from this his appetite is still quite good Obviously such a complaint would arouse a suspicion of carcinoma of the stomach

In all cases of Addisonian pernicious anaemia there is complete achylia i e absence of hydrochloric acid and of ferments from the gastric juice A few cases of what have been alleged to have been true pernicious anaemia in which free acid has been present in the stomach have been described but the diagnosis of these is in fact doubtful

Radiographically the stomach usually presents some degree of excessive peristalsis while the rugae of the mucous membrane are flattened or have even disappeared

The gastroscopic appearances of the stomach are interesting and important although of course gastroscopy will not be performed as a routine in these cases It should however be carried out if there is the least suspicion of carcinoma of the stomach

The appearances seen through the gastroscope are usually striking Thus there is some degree of atrophy of the mucous membrane This may be generalized or more commonly patchy The affected areas present an appearance which has been compared with that of mother of pearl There seems no doubt that the longer the patient has been suffering from pernicious anaemia the more extensive is the atrophy of the mucous membrane

It is important to realize that the atrophy particularly affects the vertical portion of the stomach together with the fundus while the horizontal prepyloric part is often practically normal The incidence of carcinoma of the stomach is probably higher in sufferers from pernicious anaemia than in the general population and every patient who has suffered from the disease for a number of years should have regular investigations of the stomach It is interesting that the incidence of cancer of the stomach in sufferers of pernicious anaemia is approximately equal in the two sexes whereas in the general population it is more common in males

Symptoms of intestinal upset are common Occasionally there is persistent diarrhoea which is not accompanied by pain or by mucus or blood in the stools More commonly there is a history of alternating diarrhoea and constipation

As a megalocytic hyperchromic anaemia can be caused by various intestinal parasites it is necessary in those patients who may have become infested with intestinal worms to search for these in the faeces

The diarrhoea of uncomplicated cases is completely relieved by treatment of the anaemia

Nervous System

The neurological disorders that may accompany pernicious anaemia are common and numerous but there is much controversy as to their frequency If even the slightest nervous disturbances are included it is probably true to say that they will be found in quite 90 per cent of cases

The slighter complaints are of tingling especially in the toes and fingers and of formications most commonly in the region of the calves These may be accompanied by slight disturbances of gait due to diminution of sensation in the soles of the feet

At this stage the only other objective change detectable in the nervous system is decrease of vibration sense over the malleoli and perhaps the lower part of the tibiae

Such minor disturbances disappear completely soon after the start of suitable treatment of the pernicious anaemia

A much more important neurological complication is *sub acute combined degeneration of the spinal cord* This malady may sometimes become manifest before anaemia is present or it may develop at any stage of the anaemia although there is no direct relationship between the severity of the two conditions It may also develop during the course of treatment and even after the blood picture has

been maintained at an *almost* normal level for months or even years It may be emphasized here that no case of pernicious anaemia can be regarded as being immune from the development of sub-acute combined degeneration of the spinal cord unless the blood is main tained at normal or higher levels without intermission by adminis tration of potent liver extract or of vitamin B 12

It would appear that sub acute combined degeneration of the spinal cord is in some sense the effect of malnutrition of the spinal cord and some substances appear to expedite its development e g folic acid (p 70)

The development of sub acute combined degeneration can roughly be divided into three stages although admittedly these overlap

Briefly the initial symptoms are mainly functional and subjective being similar to or identical with those mentioned above In addition however there may be hypoaesthesia of glove and stocking distribution usually more marked in the lower extremities There may be fleeting pains especially in the legs and girdle pains may occur

There is slight impairment of finer movements and women often complain that it is difficult to thread a needle while at the same time there may be slight ataxia Deep sensibility is often slightly impaired but the reflexes at this stage may be normal although the knee jerks are sometimes increased

If vigorous treatment is not undertaken at this stage the nervous syndrome inevitably progresses and signs of inco ordination develop sooner or later The gait is not particularly unsteady but presents a mixture of ataxia and spasticity Romberg s sign is positive and these patients are liable to fall in the dark

As a rule the upper limbs are less affected than the lower and there may be a remarkable resemblance to cerebellar disorders

Paresis progresses particularly in the lower limbs the muscles often being hypertonic for a time the reflexes may be exaggerated especially the knee jerk while the ankle jerk is decreased Babinski s sign is almost invariably present indicating interference with the pyramidal tracts

There is little or no diminution of superficial sensation but deep sensibility is greatly diminished

Painful episodes of the nature of lightning pains become frequent and may even simulate the gastric crises of tabes Indeed there may be a considerable resemblance to tabes but at this stage there are neither trophic nor sphincter troubles

The advanced stage of sub-acute combined degeneration which

is now rarely seen is that of flaccid paraplegia with disappearance of reflexes gross weakness of the sphincters and severe trophic changes in the skin particularly of the legs

It must be realized that patients may present a fairly acute flaccid paraplegia at a time when no anaemia is clinically detectable This is almost the only example of paraplegia due to sub-acute combined degeneration that is ever seen at the present time

Mental disturbances often extremely slight are very common in the course of Addisonian anaemia Again it is difficult to present accurate statistics because different observers employ different criteria but if one includes even the slight changes there can be no doubt that some mental change is found in quite 50 per cent of cases

Commonly there are slight changes in the form of mental depression more or less proportional to the degree of physical weakness and this is often associated with slight weakness of mental concentration and sometimes headache and insomnia

More clearly defined syndromes are not common and may occur in association with sub-acute combined degeneration of the cord or independently of it There is however no pathognomonic picture in the neuroses and psychoses that may accompany pernicious anaemia Any form of psychosis may develop but in the majority the prognosis is good if the anaemia is the precipitating cause of such psychological changes and one often finds that the patients were previously of somewhat unstable personality

Variations in the Clinical Picture of Pernicious Anaemia ✓

A relatively small number of cases of Addison s anaemia present themselves with symptoms suggestive of carcinoma of the stomach viz dyspepsia anorexia and loss of weight The absence of glossitis and as a general rule of icterus in cases of cancer is strongly in favour of a clinical diagnosis of pernicious anaemia

Radiographic examination will not always enable a differentiation to be made because in pernicious anaemia the stomach may present a polypoid appearance rather suggestive of a fungating cancer Gastroscopy will probably enable a differentiation to be made in every case

A second clinical type of pernicious anaemia is that which presents itself with persistent diarrhoea which in some cases may be of several years duration A suspicion of sprue may then be aroused but the diarrhoeic form of pernicious anaemia is in fact a syndrome distinct from that disease

Splenomegaly is rarely sufficient to be noticed by the patient but

occasionally discomfort and a sense of weight in the left hypochon drium may call the patient s attention to his illness

Pernicious anaemia may develop with a considerable rise of temperature sometimes accompanied by slight jaundice

Such a picture may result from an intercurrent infection in a patient with initially only a mild anaemia which is aggravated by the infection But apart from this there do exist cases in which the onset appears to be acute thus resembling an acute haemolytic anaemia

Ocassionally there may be resemblances between pernicious anaemia and nephritis in that the patient presents severe generalized oedema This may be due to the disease itself or to complicating nephritis or to myocardial weakness

Neurological symptoms may be the first to call attention to the existence of the disease at a time when the anaemia is very slight or even absent It is therefore extremely important to be well ac quainted with the various nervous manifestations of Addison s anaemia

In the past a haemorrhagic form of pernicious anaemia was described but it appears that there was some confusion of thought and at the present time the general view is that haemorrhages of any severity do not occur except in the most advanced untreated cases

Blood Picture

The essential feature of the blood in true pernicious anaemia is a greater reduction in the number of red corpuscles than in the amount of haemoglobin That is to say on the average each red corpuscle contains more haemoglobin than normal As normal corpuscles are fully saturated with haemoglobin it is obvious that any increase in their content of this substance must be associated with an increase in size Also there is considerable variation in the size of the red cor puscles (anisocytosis) varying from extremely small ones (micro cytes) to forms much larger than normal (megalocytes) The last named are the corpuscles that are characteristic of Addison s anaemia and are most numerous in the more severe stages

The most striking method of demonstrating anisocytosis and megalocytosis is by the Price Jones curve (Fig 4)

The work involved in the preparation of the curve is very great and it is usual to be satisfied with the determination of the average diameter of the red corpuscles as estimated by a diffraction method e g the Eve halometer It is then found that the mean diameter is in the region of 8 microns or more as compared with the normal of 7 2–7 5 microns and of less than 7 microns in the hypochromic

microcytic anaemias The Wintrobe indices are all of great diag nostic significance but are not carried out as a routine in this country

The second striking feature of the red corpuscles is abnormality of shape (poikilocytosis) Bizarre forms may be found some resem bling a hand mirror others a comma and so forth Poikilocytosis is most marked in the severe stages of the disease but it must be realized that abnormally shaped red corpuscles are found in other anaemias also although less constantly and in smaller numbers

An appreciable number of corpuscles stain a bluish tint (poly chromasia) but these are never numerous except in the early stages of treatment

Polychromatic corpuscles are slightly immature and there is no doubt that such immaturity is better demonstrated by vital staining when the polychromatic corpuscles are revealed as reticulocytes (p 27)

Other abnormalities of the red corpuscles are of less diagnostic importance thus some may contain chromatin particles or even basophilic dots It is important to realize that punctate basophilia may occur in any form of anaemia and is not pathognomonic of lead poisoning

A variable number of nucleated red cells can be found in the blood These are most numerous in the most severely anaemic stages when the majority are typical normoblasts The only type of nucleated red cell which is characteristic of Addison s anaemia is the *megalo blast* This large nucleated red cell with a reticular nucleus is very rarely plentiful in the blood even in untreated cases but a sufficiently prolonged search will always reveal the presence of a few Before the introduction of various methods of mensuration the discovery of megaloblasts in the peripheral blood was almost essential for diag nosis but to day their discovery is of interest although of no great importance

The nature of the megaloblast and its relation to the normoblast has been and still is a subject of controversy which has a little practical importance A very brief summary will suffice here

As will be seen from the schema on the frontispiece the normal course of development of red corpuscles is through a developmental series extending from the marrow reticulum-cell through the pro erythroblast the normoblasts of various stages of maturity to the reticulocyte and so to the red corpuscle If there is a deficiency of haemopoietic factor a different series of developmental changes ensues Thus instead of the formation of a pro erythroblast from the marrow reticulum-cell there is development of a pro megaloblast

which passes through various stages of maturation comparable with those of the normoblastic series until the final stage that of a large but fully haemoglobinized corpuscle This is properly called a *megalocyte* although unfortunately the name macrocyte is often applied to all large corpuscles In fact the name *macrocyte* should be reserved for large corpuscles that are formed by premature loss of the nucleus of large normoblasts The distinction has importance because megalocytic anaemias are due to deficiency of haemopoietic factor and are properly treated by its administration whereas macrocytic anaemias are not improved by administration of liver extract or of vitamin B 12 There is much confusion in the minds of practitioners because of the indiscriminate use of the two terms as synonyms

The leucocytes are constantly reduced in number the values usually lying between 2 000 and 5 000 per c mm the lowest figures occurring in the most severe cases

In an otherwise typical case of pernicious anaemia the presence of leucocytosis is suggestive of the presence of an intercurrent infection while in doubtful cases leucocytosis may suggest that the diagnosis is incorrect e g that the anaemia is not primary but is due to some other condition such as carcinoma of the stomach

The reduction in the total number of leucocytes is due to neutropenia while the absolute number of lymphocytes remains normal

Large neutrophils with excessively segmented nuclei can invariably be found while in severe cases there may in addition be a few immature leucocytes e g myelocytes in the peripheral blood

Eosinophils and monocytes are reduced in number in untreated cases

A moderate degree of thombocytopenia is common while a few extremely large misshapen platelets can always be found

The Bone Marrow

An examination of the bone marrow during life e g by sternal puncture is probably the most accurate method of making a diagnosis of pernicious anaemia in patients who have not yet received treatment The essential and striking character of the marrow is the presence of large numbers of megaloblasts such as are never seen in normal marrow These elements rapidly disappear when adequate treatment is undertaken and this fact explains the need for marrow puncture to be undertaken *before* any haemopoietic factor is given

When adequate amounts of haemopoietic factor are administered megaloblasts rapidly disappear from the marrow while at the same

time the excretion of uric acid rises sharply Clearly the megalo blasts are destroyed and normoblastic blood formation takes its place There is no sound evidence that megaloblasts supplied with haemopoietic factor are converted into normoblasts

The marrow also shows signs of abnormality in the formation of leucocytes and platelets Some of the former are so called giant metamyelocytes which are presumably the parent cells of the hyper segmented neutrophils while there may also be abnormal mega karyocytes

The essential feature of the myelogram is however the presence of an overwhelming number of megaloblasts

Haematological Variants of Pernicious Anaemia

As a general rule it may be said that the blood picture of pernicious anaemia is so striking as to be pathognomonic There are however occasionally cases in which megaloblasts are transiently so numer ous in the peripheral blood that the haematologist unguided by clinical acumen might well imagine that he was dealing with a case of Di Guglielmo s disease (p 153)

An important and confusing variation is the so-called *dimorphic anaemia* in which owing to a concomitant deficiency of iron the colour index is low although the characteristic megalocytosis is present Such a blood picture may occur in ill nourished persons or may develop in the later stages of treatment when the available stores of iron in the tissues have been exhausted by the active forma tion of haemoglobin

Finally it should be mentioned that pernicious anaemia can and should be diagnosed at a time when there is neither reduction of red corpuscles nor haemoglobin This occurs particularly in those cases in which neurological symptoms occur early Even at this stage the characteristic megalocytes and the hypersegmentation of neutrophil nuclei can be detected in the peripheral blood while megaloblastosis in the marrow is already well developed

Treatment

The discovery by Minot and Murphy of the value of a diet rich in liver in the treatment of pernicious anaemia completely altered the outlook in this previously fatal disease It was soon found however that no patient could tolerate the ingestion of large amounts of un cooked or almost raw liver for long periods of time and many attempts were made to produce concentrated extracts which would contain the essential haemopoietic principle Later even more

concentrated extracts suitable for parenteral injection were prepared and until recently this was the most satisfactory method of treating pernicious anaemia

It was supposed that in the normal person an intrinsic factor in the stomach interacted with an extrinsic factor which was stored in the liver In pernicious anaemia there was supposed to be absence or deficiency of intrinsic factor and therefore failure to produce an adequate amount of haemopoietic factor This however could be supplied by injections of liver extract

An alternative method of treatment that was developed in the history of our modern knowledge of pernicious anaemia was the administration of dessicated hog s stomach by mouth This was supposed to contain freshly formed haemopoietic factor but as a rule intra muscular injection of liver extract was the method of choice

Blood Changes during Treatment

At this point it will be useful to discuss briefly the blood changes which are indicative of efficacious treatment

Thus three or four days after commencement of treatment there should be a rise in the number of immature red cells which is best detected by enumeration of the reticulocytes After large doses of potent liver extract are given the reticulocytes commence to rise within forty eight hours and reach their maximum in about 120 hours The percentage then begins to fall and the mature red cor puscles start to rise but it is not until about the end of two weeks that this increase is at all striking but within four to eight weeks it should be possible to restore the haemoglobin and red corpuscles to normal levels Occasionally the colour index falls after the blood picture has otherwise become normal presumably because the iron storage depots have been greatly depleted and it is then necessary to give iron by mouth

Many attempts have been made to standardize liver extracts but until recently there was no chemical method available while stan dardization by injection of liver extract into experimental animals was useless because it was impossible to produce pernicious anaemia in them

Various units of liver extract have been produced and these have usually been based on the average expected maximum reticulocyte percentage following daily intramuscular injection of the liver extracts The unit of the United States Pharmacopoeia represents the minimal amount of the extract which when given daily in an

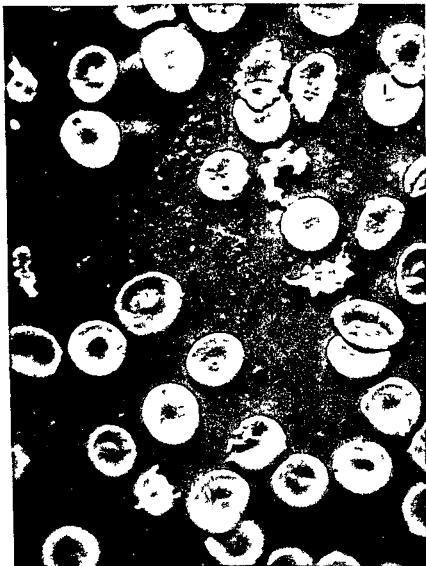


FIG 6 —Target corpuscles (shown by the method of ombrage) Several target (Mexican hat) corpuscles are clearly seen together with some extremely bizarre poikilocytes (*by courtesy of Dr M Bessis Centre National de Transfusion Sanguine Paris*)



FIG 7 – X ray of hand from a case of osteopetrosis The extreme density of the bones is shown The distal parts of the digital phalanges have been converted into solid bone as have the lower ends of the radius and ulna

uncomplicated case of pernicious anaemia produces an average reticulocyte response which can be calculated from the official charts This is not entirely satisfactory because occasionally the reticulocyte response is relatively poor and yet the red corpuscles and haemo globin subsequently rise rapidly For this reason it is customary in Great Britain and Canada to attribute more importance to the rise of the red corpuscles and haemoglobin than to the reticulocyte response The Canadian unit of liver extract is defined as being one seventh of the weekly dose required to produce a satisfactory rise in the red cell count average weekly increase in red cells during the first two weeks= 0 93–0 214 of the red cell count before treatment

The standard routine treatment of pernicious anaemia is still the injection of adequate amounts of potent liver extract or of vitamin B 12 starting with quantities sufficient to produce a maximal reti culocyte response and continuing with maintenance doses that prevent the red corpuscles from falling below five million per c mm and the haemoglobin below 98 per cent

The substance now known as vitamin B 12 was extracted in minute amounts from raw liver and was supposed to be the essential haemopoietic (anti pernicious anaemia) factor *Injection of minute* amounts of this substance evoke a reticulocyte response which is fol lowed by a rise of red corpuscles and haemoglobin It is true to say that vitamin B 12 produces effects identical with the most potent liver extracts but there is now some reason for assuming that it is not the haemopoietic factor itself but is perhaps extrinsic factor the absorption of which is facilitated by adequate amounts of intrinsic factor Whatever may be the true explanation there is no doubt that it is simpler and more satisfactory to treat cases of pernicious anaemia by injections of B 12 starting with a dose of 20 micro grammes and using 10 microgrammes at intervals of two or three weeks for maintenance treatment

Fortunately B 12 can be obtained as a by product in the growth of streptomyces hence its cheapness

A great advantage of B 12 is that it is free from protein and that therefore there is no danger of allergic phenomena following its injection This is not a common complication of liver treatment but when it occurred caused great difficulties These are now obviated by the use of vitamin B 12

A peculiar substance present in large amounts in spinach and some other green vegetables is capable of evoking a reticulocyte response followed by restoration to normal of the blood picture in cases of pernicious anaemia This factor has been synthesized and is

known as folic acid It is however not to be regarded as the ideal or even the proper treatment for pernicious anaemia because unlike liver extract and B 12 it does not protect the central nervous system against sub-acute combined degeneration nor does it produce any improvement in that condition if it has already developed

The treatment of pernicious anaemia should be by injection of potent liver extract or perhaps preferably of vitamin B 12

It is not possible to plan a rigid scheme of treatment but certain general principles can be laid down Thus once a diagnosis of pernicious anaemia has been made 20 microgrammes of B 12 or 4 c c of a potent liver extract should be injected on alternate days for ten days Then an injection of the same amount at weekly intervals should be given until the red corpuscles have reached 5 million per c mm and the haemoglobin 100 per cent If at any time the colour index falls greatly it will be necessary to give iron by mouth

When the blood picture has become completely normal a maintenance dose must be given at intervals In most cases 10 microgrammes of B 12 or 2 c c of a potent liver extract once every three weeks will suffice but as the degree of deficiency varies somewhat from case to case the exact dosage and the intervals between injections have to be found by experiment

It is essential to realize that the maintenance dose required may gradually increase It is therefore necessary to examine the patient s blood at intervals and to increase the dose if there is any indication of the least deterioration

The development of intercurrent infections if of any severity necessitates temporary increase in the dosage as otherwise the red corpuscles and haemoglobin will fall Apart from this cause another extremely important one is the development of arteriosclerosis Thus as patients with pernicious anaemia get older it is often necessary to increase the maintenance dose

Very rarely the response to B 12 or potent liver extract is or becomes less satisfactory and apart from the above mentioned interfering factors the important one is the existence of slight degrees of hypothyroidism Until this condition is rectified neither liver extract nor B 12 however large the dose will restore the blood picture to normal

Prognosis

In the absence of complications the prognosis of adequately treated pernicious anaemia is uniformly good although not all the abnormalities disappear The blood and bone marrow pictures

return to normal and must be kept at these levels The atrophied papillae of the tongue gradually take on normal appearances although it may be months or even a year or two before the tongue is restored to normal The gastroscopic changes retrogress to some extent by the appearances never become completely normal and there is rarely if ever restoration of acid secretion perhaps because the achlohydria is of constitutional origin

Although the prognosis of treated pernicious anaemia is good there does appear to be an excessive liability to the development of carcinoma of the stomach This event is however relatively uncommon but the possibility should be borne in mind in the more elderly patients

The prognosis of the nervous complications is often difficult to assess In cases in which the nervous symptoms are due entirely or mainly to peripheral neuritis intensive treatment of the anaemia will result in their disappearance When however there are organic changes in the central nervous system complete restoration to normal is as a rule impossible Even so intensive treatment with injections of potent liver extract or of vitamin B 12 in amounts larger than those required to maintain the blood at normal levels is often followed by a surprising degree of improvement This may be so great that patients bed ridden because of spastic paraplegia may again be able to walk although spasticity does not completely disappear

In the absence of grave complications it would appear that the expectation of life of adequately treated cases of pernicious anaemia is somewhat higher than that of normal persons of the same age group

CHAPTER VII

ANAEMIAS DUE TO DEFICIENCY OF A SPECIFIC HAEMOPOIETIC SUBSTANCE—*continued*

ADDISONIAN pernicious anaemia is not the only example of megalocytic hyperchromic anaemia Similar blood and marrow pictures may occur in association with a number of identifiable pathological conditions which are sometimes known as para Addisonian anaemias or perniciosiform anaemias

Although the exact status of intrinsic factor extrinsic factor and haemopoietic factor which seemed to be clearly known, is now again a matter for discussion it is practically convenient to accept the view that such para Addisonian anaemias may be due to deficiency or failure to utilize any one of these factors

Anaemia Associated with Steatorrhoea

There are three main disorders in which there is gross loss of fat in the faeces and which may lead to the development of hyperchromic macrocytic anaemia These are *sprue idiopathic steatorrhoea* and *coeliac disease* Some authors regard these three conditions as belonging to the same group and make no clear distinction between them It is however convenient to separate them as far as possible

Sprue

This term refers to a chronic wasting disease of tropical countries and is characterized by glossitis diarrhoea with pale bulky frothy ill smelling stools The disease is much commoner in white inhabitants in the tropics than in natives and its incidence appears to be greatest in those who have spent the longest time in hot climates

Symptoms

There is often a history of chronic indigestion with flatulence and alternating constipation and diarrhoea for many months or even years before the fully developed syndrome is observed At some stage often quite early there is soreness of the tongue anorexia and mental depression

Painful fissures may develop in the oesophagus and also in the region of the anus These may precede or accompany the fully developed syndrome

Although anaemias of pernicious type may develop with marrow changes essentially like those of Addisonian anaemia sub-acute combined degeneration of the spinal cord does not occur

X ray examination of the gastro-intestinal tract shows an almost characteristic appearance in which a portion or several portions of the small intestine show a peculiar moulage sign after a barium meal

The term moulage is used because instead of the normal feathery appearance of the duodenum and upper half of the jejunum there is a characteristic appearance which may resemble a tube into which wax has been poured and allowed to harden This depends upon atrophy of the valvulae conniventes Indeed the small intestine may be dilated to a size as great as that of the colon

Gastroscopy shows some degree of atrophy of the stomach but the mother of pearl plaques of true pernicious anaemia are never seen

The Blood and Marrow

Anaemia is not invariable and when it is present it may be hypochromic microcytic or more commonly hyperchromic and megalocytic The latter type often develops in cases which for a considerable time have been hypochromic In these cases the blood picture is much the same as that of true pernicious anaemia although poikilocytosis is less striking The myelogram is also essentially the same Giant metamyelocytes and polymorphs with hyper segmented nuclei are present but the degree of megaloblastic transformation of the marrow is less than in Addisonian anaemia some normoblastic erythropoiesis always being preserved

Moderate reduction in the number of platelets is common but occasionally especially when the anaemia is very severe the platelets may be so low as to lead to purpura

Diagnosis

Diarrhoea steatorrhoea and other signs indicative of nutritional deficiency in persons in or who have been resident in tropical climates form the essential diagnostic features It must be remembered however that there may be quite severe steatorrhoea without any diarrhoea Even so a para Addisonian anaemia may develop in these cases

The asthenia hypotension and pigmentation which may develop

in long standing cases may lead to confusion with Addison s disease of the suprarenals

Pathogenesis

The causation of hyperchromic macrocytic anaemia in sprue is not entirely understood It is possible perhaps probable that it is due to excessive loss of extrinsic factor in the motions As however the causation of the steatorrhoea is not fully understood it follows that the aetiology of sprue itself is still obscure

Treatment

The treatment of the hyperchromic macrocytic anaemia of sprue is much less successful than that of true pernicious anaemia Certainly the injection of highly purified liver extracts which is so efficacious in true pernicious anaemia is much less so in sprue The same is true of injections of vitamin B 12 and as this substance is now usually regarded as being extrinsic factor it seems clear that the older theory of the genesis of the anaemia is not true

The haemopoietic defect is of the same type as that in true pernicious anaemia but the nutritional abnormality affects erythropoiesis at a different level This is shown by the administration of folic acid which relieves the glossitis and diarrhoea in almost every case while at the same time leading to a reticulocyte crisis which is followed by *a rise in the red corpuscles and haemoglobin Oddly enough* the fat content of the stools is not always restored to normal

Folic acid may be given by intramuscular injection in doses of 15 mg daily but the results of oral administration are practically as satisfactory This is the essential treatment but in addition other vitamins should be given because of the general nutritional deficiency that has developed as a result of the persistent diarrhoea The blood picture is sometimes confused by a concomitant iron deficiency and one then finds a megalocytic but hypochromic anaemia (a so-called dimorphic anaemia) When this is present administration of iron is essential

Idiopathic Steatorrhoea

The main perhaps the only difference between this condition and sprue is that it may develop in the inhabitants of temperate climates who have never visited the tropics Diarrhoea is less severe glossitis is less intense and general nutritional deficiency is less marked than in tropical sprue while the concomitant anaemia is more frequently hypochromic than hyperchromic

Treatment

Treatment is on the same lines as of the anaemia of sprue viz administration of iron and vitamins in the hypochromic cases folic acid and vitamins in the hyperchromic cases and of iron together with folic acid in the dimorphic ones

Coeliac Disease

This syndrome is similar to that of sprue and idiopathic steatorrhoea but there are differences depending mainly on the age of these patients

Coeliac disease develops in young children who present the common symptoms of sprue and the allied diseases together with other signs of nutritional deficiency especially of the skeleton These take the form of osteoporosis stunting of growth occasionally spontaneous fractures and even infantilism The explanation of these changes is of course the persistent loss of calcium from the body of a growing child

There may be some of the ordinary signs of iron deficiency anaemia e g brittle spoon shaped nails lustreless hair and a mournful expression Affected children usually look younger than their age and indeed this is sometimes the case in adults suffering from idiopathic steatorrhoea

Loss of weight is often severe and the di tended small intestine may be visible through the atrophied abdominal wall For some unknown reason advanced atrophy of the buttocks is so common as to be almost pathognomonic

The above changes are similar to but not identical with those of osteomalacia

Blood Picture

The anaemia of coeliac disease is most commonly of the iron deficiency hypochromic microcytic type but occasionally particularly in prolonged cases the anaemia becomes hyperchromic and megalocytic although the megalocytosis is less striking than in true pernicious anaemia In these cases there is some degree of megaloblastic transformation of the marrow but this is less intense than in sprue and of course than in true pernicious anaemia

Treatment

This is less satisfactory than in sprue or idiopathic steatorrhoea but administration of iron and of folic acid often leads to considerable improvement although it is rare for a case of coeliac disease to be cured

In general then the treatment of coeliac disease is the administration of iron and of folic acid the latter being of value even in the cases in which the anaemia is hypochromic perhaps because of its effect on the absorption of fat from the intestine In addition vitamin supplements of all types are essential

It is interesting that in some cases of sprue and in a fair number of cases of idiopathic steatorrhoea there is a history of intermittent diarrhoea in childhood There is thus some reason for regarding the three main types of steatorrhoea as being aetiologically related to one another

Steatorrhoea in General

Either hypochromic or less commonly hyperchromic anaemia may accompany any type of chronic steatorrhoea e g that due to chronic pancreatic disease malignant infiltration of abdominal lymphatics or gastric colic fistula

Megalocytic Hyperchromic Anaemia Associated with Malnutrition

This condition which is so much commoner in hot climates is sometimes known as tropical macrocytic anaemia It resembles Addisonian pernicious anaemia both clinically and haematologically but its aetiology is different

The first cases that were described were in pregnant native women in India but later an identical condition was found in non pregnant women and even in men

Clinically the main complaints are those common to all forms of anaemia together with soreness of the tongue and mouth diarrhoea and varying degrees of oedema The spleen is frequently palpable but is never greatly enlarged and signs of complicating disease of the central nervous system practically never occur This is of course a distinction from pernicious anaemia as is also the fact that achlorhydria is not especially common in this disease As a rule there is no detectable jaundice and the serum bilirubin is not above normal levels unlike the invariable state of affairs in true pernicious anaemia There is however a similar anaemia of the tropics in which there are some signs of an increased blood destruction It is however uncertain whether these cases are identical with those first described by Wills

Blood

The picture is the same as that in pernicious anaemia viz megalocytosis poikilocytosis and leucopenia while the bone marrow

shows partial megaloblastic transformation The platelets are at or below the lower limits of normal and purpura is not uncommon

Aetiology

Whether all these cases are to be regarded as one disease or not is less important than is the fact that they have a common aetiology viz. dietary deficiency especially deficiency of animal protein The dietetic poverty may also include deficiency of iron hence a megalocytic hypochromic (dimorphic) anaemia is quite common

Treatment

In the absence of concomitant diseases such as chronic malaria and infestation with intestinal worms the anaemia can be rapidly relieved by the oral administration of yeast marmite or lightly cooked liver Parenteral administration of more or less crude liver extracts is equally effective but the very highly refined extracts which have proved so valuable in Addisonian anaemia are quite ineffective in most of these cases It would appear that there is a deficiency of some haemopoietic principle different from that responsible for pernicious anaemia

Not uncommonly an anaemia of this sort is precipitated by increased nutritional requirements hence the frequency of its development during pregnancy

Pellagra

Here is another example of a clinical syndrome which is primarily due to nutritional deficiency such as occurs in a population whose staple diet is maize

Most commonly the anaemia that occurs in pellagra is hypochromic and microcytic but hyperchromic megalocytic cases are well known This is however not identical with pernicious anaemia as is shown by the fact that intrinsic factor is present in the gastric juice as is also hydrochloric acid It appears therefore that this is another example of a pernicious like anaemia due to an exogenous nutritional defect

Pernicious Anaemia of Pregnancy

Owing to the age incidence of Addisonian anaemia pregnancy is rarely observed in these patients but there is a megalocytic hyperchromic anaemia which may occur in pregnant women generally but by no means invariably of the poorer classes whose diet has been insufficient.

The blood picture is in general terms similar to that of Addisonian anaemia but there is less anisocytosis and poikilocytosis while the degree of megaloblastosis in the marrow is relatively slight The major part of the erythropoietic process remains normoblastic in type

The nature of the so called pernicious anaemia of pregnancy is uncertain and it appears probable that a variety of syndromes is included under this heading For this reason no routine treatment can be advocated Some cases will respond to large quantities of crude liver extract or of yeast given by mouth, whereas others are so severe as to require blood transfusion in order to tide the patient over until an adequate response to liver treatment occurs There are however cases which do not respond to any method of treatment other than transfusion In a few cases spontaneous recovery occurs after delivery but it is unsafe to await this event in the severe cases transfusions are essential of course together with an adequate diet

Megalocytic Hyperchromic Anaemia associated with Organic Abnormality of the Gastro Intestinal Tract

Stomach

Hyperchromic megalocytic anaemia has been described as occurring in association with cancer or polyposis of the stomach presumably because extensive destruction of the mucous membrane leads to lack of formation of intrinsic factor A very small proportion of patients on whom *gastrectomy* has been performed have developed the typical blood and marrow picture of pernicious anaemia This is extremely rare perhaps because the patients do not survive sufficiently long On the other hand hypochromic anaemia of the iron deficiency type is very common in these cases

Hyperchromic megalocytic anaemia may develop after *gastroenterostomy* usually after very long periods e g fifteen to twenty years Here the aetiology is rather obscure It may be that extrinsic factor intrinsic factor or even haemopoietic factor itself is so rushed through the stoma that there is insufficient time for ab orption One difficulty in explaining the causation of these cases is that they do not all respond equally well to the routine treatment for pernicious anaemia In the majority of cases injections of potent liver extract or vitamin B 12 are followed by a reticulocyte crisis and if treatment is maintained there is a gradual rise of the blood picture to normal and conversion of the myelogram to normal There are however cases in which only partial recovery from the anaemia occurs with such

treatment and some of these cases can be restored to normal by the oral administration of folic acid even when liver extracts have failed In such circumstances one finds that there is a moderate reticulocyte crisis in the early stages of the liver treatment and a second reticulo cyte crisis soon after the commencement of treatment with folic acid

Intestinal strictures are occasionally accompanied by the blood and marrow picture of pernicious anaemia even although there is free hydrochloric acid present in the gastric juice

Megalocytic Hyperchromic Anaemia in association with Disease of the Liver

Extensive hepatic disorder especially in the form of advanced cirrhosis may be accompanied by a moderately severe anaemia of the pernicious type perhaps because of failure of the damaged liver to store haemopoietic factor in adequate amounts

The anaemia is less severe than the Addisonian type and poikilocytosis is much less marked

Treatment is not very satisfactory and must be directed to supply ing sufficient amounts of haemopoietic factor in the form of potent liver extracts or vitamin B 12 Because of the failure of the storage mechanism the injections have to be given extremely frequently

Hyperchromic Anaemia due to Infestation with the Fish Tapeworm

In the small proportion of persons infested with the fish tapeworm Diphyllobothrium latum a clinical and haematological picture identical with Addisonian anaemia develops

This tapeworm is only commonly found in Finland and round the Great Lakes in America although occasional cases of infestation have been observed elsewhere Clearly then as a general rule one ignores this possibility in cases of pernicious anaemia except in countries where the worm is endemic

By no means all people infested with the worm develop a hyper chromic megalocytic anaemia Indeed it has been held that it is only in persons predisposed to the development of Addisonian anaemia that the worm will evoke a full picture of that anaemia This idea is supported by the fact that the incidence of idiopathic pernicious anaemia appears to be higher in the relatives of persons with diphyllobothrium anaemia than in the general population

That the anaemia whatever its exact causation may be is indeed identical with pernicious anaemia is shown by the fact that in un treated cases sub acute combined degeneration of the cord may develop and by the fact that treatment with potent liver extracts or

vitamin B 12 will restore the blood picture to normal even when the worm has not been expelled

On the other hand anthelmintic treatment without administration of liver extract is followed by gradual restoration of the blood picture to normal with very little or no tendency to subsequent relapses It seems probable therefore that the worm in the intestine destroys extrinsic factor and perhaps also interferes with absorption Thus when liver extract is administered in large amounts there is insufficient both for the worm and the host

There must be many cases of tapeworm pernicious anaemia which have never been recognized and have been regarded as being examples of Addisonian anaemia because the response to treatment has been complete

It is unfortunate that this helminthic infestation is not accompanied by eosinophilia and that its diagnosis therefore must depend upon routine examination of the faeces

Achrestic Anaemia

This rare condition is clinically identical with pernicious anaemia but fails to respond to the same treatment although liver extract or vitamin B 12 may evoke a slight reticulocyte increase The marrow picture is predominantly megaloblastic and remains so in spite of treatment Free acid is present in the gastric juice and at autopsy there is no deficiency of haemopoietic factor in the liver (see Plate I, fig 1)

The disease runs a long but always fatal course Temporary improvement follows transfusion while folic acid and all the other remedies used in pernicious anaemia should be tried In some cases improvement has followed oral administration of proteolysed liver even when injections of liver extract have failed

Probably achrestic anaemia is a concept under which different maladies are subsumed For this reason some writers include it in a group of diseases pusillanimously called *refractory anaemias*

General Note on Anaemias in which the Average Diameter of the Red Corpuscles is Increased

Red corpuscles larger than normal can arise in at least two ways

(i) when there is deficiency of haemopoietic factor red corpuscles are derived from abnormal ancestors Both the parent-cells and the corpuscles are larger than normal megaloblasts and megalocytes *respectively* The megalocytes can (and usually do) contain more haemoglobin than normal—then the blood picture is hyperchromic and *megalocytic* as in pernicious anaemia

(ii) in conditions of stress such as the very active blood formation that occurs during and after acute haemolytic crises as well as in other conditions the normal parent cells of the red corpuscles may lose their nuclei prematurely i e large normoblasts (macronormo blasts) give rise to large corpuscles which may (and sometimes do) contain an excess of haemoglobin hence the blood picture is hyper chromic and *macrocytic*

N B This distinction is often not maintained in the literature partly because the megalocyte and the macrocyte cannot be distin guished from one another in blood films Thus one often hears of pernicious anaemia as a macrocytic hyperchromic anaemia whereas it is in fact megalocytic

It is essential to keep the distinction in mind because macrocytic (as opposed to megalocytic) anaemias do not respond to treatment with liver or vitamin B 12

Of course the clinical characters of pernicious anaemia (and the real perniciosiform anaemias) usually suffice for diagnosis but far too many doctors believe the more scientific evidence of the labora tory rather than that of their own senses Here is the explanation of many (perhaps all) cases of liver resistant pernicious anaemia

CHAPTER VIII

HAEMOLYTIC ANAEMIAS

THROUGHOUT life effete red corpuscles are continuously destroyed mainly in the reticulo-endothelial tissue especially in the spleen while at the same time there is a compensatory formation of red corpuscles The term haemolytic anaemias is applied to those anaemias in which reduction in the number of red corpuscles and the amount of haemoglobin is due to excessive destruction of red corpuscles The possible causes of such a condition are very varied

Thus excessive haemolysis may be associated with

(1) Abnormality of the red corpuscles
 (a) a congenital factor as in alcholuric family jaundice
 (b) acquired as in nocturnal haemoglobinuria
(2) To the presence of haemolytic substances in the plasma in the form of
 (a) haemolysins
 (b) extrinsic poisons such as phenyl hydrazine (p 152)
(3) damage to the red corpuscles as in malaria
(4) increased activity of the spleen and other parts of the reticulo endothelium

Clinical Features of Haemolytic Anaemias in General

Acute The haemolytic process may be of sudden onset and may terminate as rapidly as it began An example of such a condition is seen in Blackwater fever in which the blood destruction is accompanied by a rise of temperature severe aching in the limbs and especially in the back and some degree of peripheral circulatory failure The output of urine is usually decreased and there may even be anuria due to blocking of the kidney tubules by precipitated haemoglobin and allied pigments Jaundice is invariable as a result of the increased amount of bilirubin in the blood

Acute haemolytic anaemia often presents a picture of a severe and overwhelming infection and occasionally it is indeed due to such a state e g septicaemia

Chronic haemolytic anaemia The clinical features of chronic

haemolytic anaemia vary greatly from case to case In the constitutional types of which alcholuric family jaundice is the best known and the most characteristic There is lemon yellow icterus which varies in intensity from time to time but never attains the severity of obstructive jaundice while it is not accompanied by the characteristic concomitants of the various types due to obstruction thus there is no pruritus tendency to bleeding or mental depression This difference in the symptomatology is due to the fact that the bile pigment which is the cause of the jaundice has not yet passed through the liver it is the so-called haemo bilirubin It differs also from jaundice due to bile that has passed through the liver (hepato bilirubin) inasmuch as it does not appear in the urine

Other clinical symptoms may be splenomegaly which varies in degree with the intensity of the haemolytic process as does the jaundice itself The liver is commonly enlarged especially during acute exacerbations This is due to reticulo-endothelial hyperplasia and for the same reason some enlargement of lymphatic glands may occur

The jaundice is accompanied by a raised icterus index in the blood while the van den Bergh reaction gives an indirect positive response indicating that the bilirubin is of the pre hepatic type (haemo-bilirubin)

If haemolysis is very severe and especially if it is of sudden onset some part of the haemoglobin will fail to be converted into bilirubin and free haemoglobin either unchanged or modified will be found in the plasma and may appear in the urine This is much commoner in acute haemolytic anaemias such as Blackwater fever but may occur in the acute exacerbations of chronic cases

Blood

The severity of the anaemia naturally depends upon the balance between blood destruction and blood formation but even if the processes are practically balanced and the anaemia is therefore slight there will be many young red corpuscles (reticulocytes) in the peripheral blood Indeed persistent high reticulocytosis is an almost invariable concomitant of all haemolytic anaemias acute and chronic

Acholuric Family Jaundice

This is a chronic haemolytic disease in which there is persistent jaundice although of varying intensity accompanied by a demonstrably increased fragility of the red corpuscles many of which are spherical instead of the normal biconcave form

The abnormality is inherited by both males and females and may be transmitted by either sex although not all the offspring are invariably affected

Clinical Features

Occasionally the abnormality may be obvious very soon after birth but usually the jaundice is not noticed until the end of the first decade of life when it is often aggravated by some intercurrent infection

There are probably many cases that are overlooked throughout life because there is no ill health and no clinical abnormality other than a sallow complexion In any case however there may be sudden haemolytic crises when the jaundice becomes much more severe and anaemia is striking If such acute exacerbations occur there is usually a rise of temperature together with all the other signs of acute haemolysis

Exacerbation of the anaemia without increase of the jaundice sometimes occurs as a result of inhibition of the marrow

The abnormality of the red corpuscles in these cases is not an isolated one and in the majority of cases other congenital abnormalities accompany it although these may occasion no discomfort For example undue shortness of the little finger a peculiar thinness of the tongue and abnormalities of ossification are quite frequent Among the latter the commonest is the so-called tower skull which results from asynchronism in the ossification of the cranial bones The radiographic changes in the skull may somewhat resemble those of sickle-cell anaemia (p 88)

As a general rule patients with acholuric family jaundice suffer little ill health but any acute infection may precipitate an acute haemolytic crisis In women however there is distinct diminution of fertility which does not appear to be due to the inborn abnormality but to the activity of the haemolytic process It is therefore often relieved by splenectomy which diminishes the intensity of haemolysis or even abolishes it

A woman of thirty two suffering from acholuric family jaundice who had been married for about nine years had had three miscarriages for which no gynaecological or serological reason could be discovered She had had only one acute haemolytic crisis at the age of twenty four and in spite of a persistently high reticulocyte count she had never thereafter been severely anaemic Splenectomy was performed and eighteen months later a normal child was born after an uneventful pregnancy

Blood

The striking feature of the blood apart from anaemia is the presence of spherical red corpuscles (spherocytes) In the haemocytometer may of the red corpuscles look smaller than normal and indeed their average diameter is decreased although their total volume is approximately normal In films the red corpuscles also appear to be small but do not present the normal central pallor i e they are obviously thicker than normal (Fig 5)

In spite of the presence of spherocytes it is sometimes found that the average diameter of the red corpuscles is greater than normal This macrocytosis is due to premature denucleation of large normoblasts Megalobloasts are never present but the macrocytosis may cause a slight resemblance to pernicious anaemia

Spherocytosis was for a long time supposed to be a congenital abnormality of the red corpuscles pathognomonic of acholuric family jaundice This is certainly untrue because spherocytes are found in other haemolytic diseases It is therefore probable that the abnormal shape of the red corpuscles is due to a congenital increase of a lytic substance present in normal serum This substance is known as lysolecithin Normally the amount of this substance is increased by the passage of the blood through the spleen The spherocytes in congenital haemolytic jaundice are less resistant to lysolecithin than are normal red corpuscles and it is possible that this substance or some similar one is the cause of the characteristic spherocytosis This view is supported by the fact that the parent cells in the marrow (normoblasts) do not show any abnormality of shape

Leucocytes In the quiescent periods the leucocyte count is at or slightly above the higher limits of normal any increase being due to neutrophilia Usually there are a few slightly immature neutrophiles e g metamyelocytes During the crises leucocytosis becomes very great indeed a leukaemoid picture may develop with many myelocytes and sometimes a few myeloblasts in the peripheral blood

Platelets There is persistent thrombocytosis which may become extreme during crises This is the explanation of the tendency to thrombosis that is sometimes very striking at these times

The bone marrow shows intense normoblastic hyperplasia with many basophilic normoblasts The only spherocytes seen are those due to admixture of peripheral blood

During haemolytic crises the normoblastic hyperplasia becomes more intense There are however occasional exacerbations of the

The abnormality is inherited by both males and females and may be transmitted by either sex although not all the offspring are invariably affected

Clinical Features

Occasionally the abnormality may be obvious very soon after birth but usually the jaundice is not noticed until the end of the first decade of life when it is often aggravated by some intercurrent infection

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The question whether splenectomy should be performed in all cases of acholuric family jaundice is a difficult one but in the view of the possibility of an acute exacerbation occurring at any time it is probably safer to advise the operation in every case The mortality is extremely small and if the operation is performed in young persons the surgical difficulties are slight When however there have been several acute haemolytic crises perisplenic adhesions may render splenectomy difficult

Splenectomy should never be performed during a crisis Transfusions can tide a patient over into the quiescent stage

Diagnosis

The increased fragility of the red corpuscles when immersed in hypotonic saline is pathognomonic of acholuric family jaundice while differentiation from acquired haemolytic jaundice (p 90) can usually be made on clinical grounds and is confirmed by the presence of antibodies in the serum in the latter disease the simplest test for these being that devised by Coombs (p 104)

Sickle-cell Anaemia

This is a severe inherited haemolytic anaemia occurring almost only in negroes and characterized by a peculiar sickle shape of the red corpuscles

The disease may remain latent throughout life the only abnormality being the peculiar shape of the red corpuscles More commonly however especially in men the abnormality is accompanied by symptoms of weakness dyspnoea pain in the back tiredness and vomiting of variable duration In some cases such haemolytic episodes occur frequently while in others months or even years elapse between them In the earlier attacks the liver and spleen become considerably enlarged and some enlargement persists even between the attacks In older patients however there is commonly fibrosis of the spleen which ultimately becomes impalpable

As in all haemolytic diseases in which acute episodes of blood destruction occur there is liability to the development of thromboses which are commonest in the small vessels of the lung and of the brain

Among other physical signs tortuosity of the retinal vessels is almost invariable

Radiographically there is usually fairly severe generalized decalcification which is particularly well seen in the vertebral bodies which may become concave as a result of such softening

In many cases even those in which no anaemia is present malleolar

anaemia not accompanied by increased intensity of the jaundice These are associated with temporary inhibition slight or severe of the erythropoietic function of the marrow by hypersplenism

Serology No antibodies play any part in causing the haemolysis of this disease which thus differs completely from so-called acquired haemolytic jaundice (p 90) As might therefore be expected the life span of healthy corpuscles transfused into these patients is normal

Complications

The main complication of chronic haemolytic jaundice is of course acute exacerbation of the condition which may even prove fatal

Another common complication which is almost invariable in prolonged cases is the presence of large numbers of small pigment stones in the gall bladder and less commonly in the bile passages These are due to precipitation from the excess of bilirubin that is excreted in the bile Frequently they give rise to no symptoms but if a large one becomes impacted in the bile duct the ordinary signs of biliary obstruction develop

Treatment

The prevention of acute haemolytic attacks is important and as these are usually precipitated by exposure to cold or intercurrent infection general care is necessary

The only method of treatment which in the very great majority of cases will result in symptomatic cure is removal of the spleen It must be emphasized that the cure is however only symptomatic the spherocytosis and increased fragility of the red corpuscles are only slightly if at all affected but the absence of the great haemolytic organ abolishes the haemolysis or at the worst reduces it so greatly as to render it insignificant

Two surgical features are of importance First accessory spleens are commoner in these patients than in the general population They should be sought for and removed at operation because if they are not one or several of them may become sufficiently hyperplastic to cause a relapse later Secondly the gall bladder and bile passages should be examined and any stones should be dealt with In young patients these are usually sufficiently soft to be crushed with the hand and then the debris will be passed along the bile duct In long standing cases however the stones may be hard and then :
sary to remove them

to persons of Mediterranean stock Like sickle-cell anaemia it also occurs in a latent form

The essential abnormality in the blood is thinness of the red cor puscles There target cells are shown in fig 6

Persons affected by the active form of the disease are often found to have at least one parent in whom the target cell trait is found although no symptoms are present

The latent form of the disease may be completely symptomless or may be accompanied by slight persistent icterus while the spleen gradually becomes more and more enlarged Often in this form of the disease target cells are numerous while another characteristic feature of the blood is as well marked as in the active form Thus the fragility of the red corpuscles in both forms of the disease is not increased as it is in acholuric family jaundice but in none of the tubes is there complete solution of the red corpuscles Even if they are placed in distilled water which of course causes complete lysis a pale gelatinous layer still remains at the bottom of the tube

Cooley s anaemia may remain latent throughout life but the off spring of such persons will have either the active or the latent form of the disease

In all other respects this rare anaemia resembles other chronic haemolytic anaemias but there is an even greater tendency to the occurrence of radiographic changes in the bones particularly striking in the skull Here the diploë presents an arrangement which is com pared with that of hair standing on end

Elliptocytosis

Occasionally the majority of red corpuscles are found to be ellipti cal instead of circular In the great majority of cases this appears to be a harmless congenital abnormality but persons so affected do appear to have a greater liability to the development of chronic haemolytic anaemia the symptoms of which differ in no way from other diseases of this group

Acquired Haemolytic Anaemias

Lederer s Anaemia

This rare form of acute haemolytic anaemia may occur at any age but seems to be slightly commoner in pregnant women It com mences more or less acutely although a week or so may elapse before the full clinical picture manifests itself

The early symptoms are high fever vomiting, headache and very severe backache There is rapid development of pallor with only a

ulcers develop and fail to heal These do not appear to be essentially different from those that may accompany other forms of splenomegaly but are much more constant

The Blood

In many cases, ordinary blood films do not reveal the characteristic sickle shape of the red corpuscles which is best demonstrated by examination of a preparation of fresh blood at reduced oxygen tension

During an acute attack the blood changes are those characteristic of any acute haemolytic condition accompanied by leucocytosis Signs of active regeneration of red corpuscles are always well marked and the reticulocytes are usually in the region of 25 per cent

In the severely anaemic stages normoblasts may be present in the peripheral blood but only the most mature of them reveal any tendency to sickling

The usual clinical signs of increased blood destruction, viz. indirect van der Bergh reaction increased icterus index and increased excretion of urobiligen are present

Prognosis

In the absence of anaemia the sickle cell trait does not appear to diminish the expectation of life but even in symptomless cases intercurrent infection may precipitate an acute haemolytic attack

The patients who are continuously anaemic and in whom cris s occur rarely live beyond middle age The cause of death may be severe anaemia but thrombosis and renal failure are common

Aetiology

All that need be said is that the sickle-cell trait is inherited as dominant and is transmitted equally by male and female This is an innate factor but whether anaemia develops or not appears to depend on exogenous causes

Treatment

No treatment is of any real value but if the spleen is extremely large splenectomy is sometimes followed by improvement although the tendency of the red corpuscles to sickling is in no way affected

Cooley s Anaemia

This is another example of a chronic haemolytic disease which is transmitted as a Mendelian dominant but which is almost confined

successfully treated by splenectomy and this operation should be performed as soon as it is found that transfusions have failed If this operation is too long delayed the outlook is bad

As already mentioned it is probable that more than one type of haemolytic disease is included in the concept of Lederer s anaemia and it is reasonable to assume that the cases in which repeated trans fusions fail represents a different disease

In some cases A C T H (25 mg four times a day) has brought the haemolytic process to a stop although the Coombs test remains unchanged The mode of action is not understood and it is still uncertain whether the cure is permanent A C T H is apparently use less in acholuric family jaundice

Acquired Haemolytic Jaundice

It has long been customary to distinguish congenital haemolytic jaundice (acholuric family jaundice) from a similar disease in which there is no family history and a very different blood picture This malady may run a sub acute or chronic course and although ob jection has been taken to the name it has the advantage of being understood by everyone

The essential feature of this disease is the presence in the blood of abnormal haemolysins which can be demonstrated in a variety of ways One of the most striking evidences is that the transfusion of healthy blood is followed by rapid destruction of the normal cor puscles This is quite unlike acholuric family jaundice in which transfused corpuscles survive a normal length of time Obviously then in acquired haemolytic jaundice the blood destruction is not due to an innate weakness of the corpuscles

Demonstration of the role played by haemolysin in this disease was later followed by the observation that although its presence could rarely be demonstrated by a simple direct test the indirect technique of Coombs shows that a haemolysin is adsorbed to the surface of the red corpuscles

The origin of the haemolysin is uncertain There seems little doubt that occasionally repeated transfusions lead to sensitization and to persistent production of haemolysins but in the majority of cases of acquired haemolytic jaundice no antigenic cause for the haemolysins can be discovered

Symptoms

No age is exempt from this disease which may manifest itself suddenly or very gradually

moderate degree of jaundice but no bile pigment in the urine then the liver and spleen become moderately enlarged and without treat ment, death occurs in the majority of cases within a few weeks or months although occasionally spontaneous recovery occurs

Blood

There is a very rapidly developing anaemia of regenerative type with reticulocytes up to 60 per cent in some cases together with a large number of normoblasts In children the average diameter of the red corpuscles is usually increased (macrocytosis) but this is not invariably so in adults It is only in cases in which spherocytosis develops that there is increased fragility of the red corpuscles

There is usually leucocytosis up to 40 000 per c mm mainly due to a great increase of granulocytes some being mature some being as young as myelocytes There are however leucopenic cases and others in which the increase of white cells is due to an excess of lym phocytes It is possible therefore that a number of different diseases are included in the concept of Lederer s anaemia

Thrombocytopenia sufficiently severe to lead to haemorrhages occurs in a small proportion of cases

Differential Diagnosis

Neither the clinical features nor the blood picture enable a diag nosis to be made easily Obviously the disease in its initial stages closely resembles septicaemia or in the haemorrhagic forms acute leukaemia The former can of course be excluded by blood culture and the latter by narrow puncture

It is much more difficult to differentiate Lederer s anaemia from an acute haemolytic crisis of acholuric family jaundice but in the latter spherocytosis is more striking while almost invariably a family history can be elicited

Occasionally an acute or sub acute haemolytic anaemia due to the presence of haemolysins in the circulating blood may very closely simulate Lederer s anaemia which differs because there is no circu lating haemolysin and the Coombs test is negative

Treatment

In what may be called true Lederer s anaemia that is to say an acute haemolytic anaemia with no haemolysins in the blood and no sensitization of the red corpuscles one or more blood transfusions almost invariably lead to complete and rapid recovery Cases in which repeated transfusions have failed to produce a cure are often

absence of haemoglobinaemia For this reason splenectomy will in some cases result in symptomatic cure That is to say the haemo lytic process will cease although in many cases the Coombs test remains positive showing that some sensitizing lysin is still adsorbed on to the red corpuscles In such cases relapse may occur at any time presumably owing to compensatory hyperplasia of the reticulo-endothelium

In a small number of cases splenectomy is followed by disappearance of the lysins and therefore by a negative Coombs test These cases are obviously completely cured

Unfortunately there is no means of assessing in advance which cases will be benefited by splenectomy It is however essential not to defer the operation too long after it has been found that trans fusions alone are insufficient

In the insidious cases there is usually little more than slowly progressive pallor and sooner or later the ordinary symptoms of anaemia together with some degree of jaundice and a positive van der Bergh reaction

In the more acute cases there is pyrexia pain in the back and often extremely severe illness

In many cases there is a history of an attack of some virus infection a few weeks or months before the onset of the haemolytic condition but whether there is in fact any relationship between the two is uncertain

In other cases such a chronic haemolytic condition has developed in tuberculous patients but again this may be coincidental

The course of the disease varies greatly from case to case In some there are long periods of spontaneous remission while in others the disease is slowly or rapidly progressive

Blood

There is no characteristic morphological blood picture Anaemia is of course invariable and may be normocytic or macrocytic Sometimes there is increased fragility of the red corpuscles while in other cases there is none The former always show well marked spherocytosis

Reticulocytosis is invariable even in the very prolonged cases in which aplasia of the marrow might be expected

A pseudo positive Wasserman reaction has often been recorded but the exact relationship of this to the circulating haemolysin is unknown

The marrow shows an intense non specific normoblastic hyperplasia

Treatment

Transfusion is essential when the anaemia is at all severe but presents great difficulties because it is essential not only to obtain blood that is compatible with that of the patient but which does not also adsorb the haemolysin at any rate to a great extent This may involve the examination of large numbers of possible donors and in some cases it is impossible to find suitable ones

Some cases show a tendency to spontaneous cure but in the majority life can only be prolonged by repeated transfusions

It is clear that the haemolysin does not destroy the red corpuscles in the circulation They are undoubtedly destroyed in the reticulo-endothelium system usually in the spleen this is confirmed by the

The anaemia is of the regenerative type reticulocytosis being considerable (up to 40 per cent)

The leucocytes mainly the polymorphs are increased during acute haemolytic episodes

The fragility of the red corpuscles to hypotonic saline is not increased

It has been shown *in vitro* that the red corpuscles of sufferers from this disease are lysed by a substance which is present in normal serum but only when the pH of the blood is decreased It is alleged that the reaction of the blood becomes slightly more acid during sleep hence the haemolysis and consequent haemoglobinuria

Whether this explanation be accurate or not there is no doubt that corpuscles from these patients transfused into normal people are destroyed more rapidly than are normal corpuscles

The two main laboratory tests for the disease are

(1) That proposed by Ham using different degrees of acidification of the test serum

(2) The heat test

Neither of these laboratory tests is really essential as the disease can be diagnosed by examination of the urine making certain that the darkness is due to haemoglobin not to myoglobin such as is found in crush injuries

Pathology

The liver may show some necrosis in the central zones of the lobules while thrombosis of the portal vein is a fairly common terminal event Haemosiderosis is as a rule not widespread and is usually confined to the kidneys which have been regarded as the site in which the haemolysis occurs

The *bone marrow* shows a simple non specific normoblastic hyperplasia

Prognosis

Many of these patients live with a varying degree of ill health for many years Death may result from widespread thromboses less commonly from extensive cerebral thrombosis or occasionally from severe anaemia

Treatment

No known treatment results in cure Various methods have been advocated and must be mentioned although most of them are extremely unsatisfactory

CHAPTER IX

HAEMOLYTIC ANAEMIAS (*continued*)

A NUMBER of rarer types of haemolytic anaemia are to be discussed in this chapter

Nocturnal Haemoglobinuria
(Marchiafava Michelisyndrome)

This rare disease is an example of excessive haemolysis associated with an acquired abnormality of the red corpuscles

Its onset is usually sudden between the ages of twenty and thirty five The first thing noticed is usually that the urine is extremely dark in the morning although normal in colour during the rest of the day The darkness is due to the presence of haemoglobin In other cases the first manifestations are explosive The patient experiences severe abdominal or lumbar pain in the morning accompanied by dark urine In either type of case pallor sooner or later manifests itself usually with a slight icteric tinge

There may be long periods of freedom from haemoglobinuria and indeed in some cases only isolated episodes occur for a period of years but sooner or later haemoglobinuria occurs every morning while in the advanced stages the urine is continuously dark

Even in the symptomless periods microscopic examination of the urinary deposits reveals the presence of granules of haemosiderin

The spleen becomes palpable but is never greatly enlarged and slight enlargement of the liver is also common The paroxysms of haemoglobinuria are not brought about by cold or exertion In the early stages of the disease the only precipitating factor appears to be sleep whether this be taken at night or during the day

The urine contains haemoglobin and methaemalbumen while the excretion of urobilinogen is also increased

Blood

A variable degree of anaemia is present in established cases This is sometimes normocytic but occasionally becomes temporarily or permanently macrocytic especially when haemolytic episodes are frequent

raised the sensitized cells are lysed by normal complement This Donath Landsteiner reaction which is easily carried out *in vitro* in the laboratory is diagnostic of the disease although other cold agglutinins are also known These have been described in association with many diseases although in the majority of cases they do not cause symptoms Such cold agglutinins may be found in atypical pneumonia glandular fever and a number of virus diseases but it is only rarely that these are the cause of an associated haemolytic anaemia In view of the fact that acrocyanosis and even gangrene of the fingers and toes may occur in paroxysmal haemoglobinuria it is interesting to note that cold agglutinins sometimes in large amounts sometimes occur in Raynaud s disease although this is rarely if ever accompanied by haemolytic anaemia

The only other changes in the blood in paroxysmal haemoglobinuria are a varying degree of anaemia of regenerative type with a fairly high reticulocytosis During the attack leucopenia is the rule and this is followed by leucocytosis

Prognosis

In well treated cases the outlook is relatively good because the severity and frequency of the attacks can be reduced although it is not common to be able to abolish them entirely

Obviously protection from cold is the essential prophylactic measure but treatment of the underlying syphilitic infection is essential This may be with arsenicals but recently better results have been reported with intensive penicillin treatment

A point of great interest is that even when anti syphilitic treatment has abolished all the symptoms and signs of paroxysmal haemoglobinuria the Donath Landsteiner reaction usually remains positive

March Haemoglobinuria

This is a rare and apparently almost harmless condition which occurs as a transient phenomenon in young males after extremely severe and prolonged exercise especially walking

After an exhausting march minute amounts of blood pigment may be found in the urine but only rarely is there frank haemoglobinuria

The pigment in the urine is certainly derived from the haemoglobin in the blood not as might be expected from the muscles

The symptoms are apparently not due to circulating haemolysin and it is alleged that the blood destruction occurs in the kidney vessels

(1) Large doses of alkali diminish *the intensity of the haemolysis* but when the treatment is stopped an extremely severe and possibly fatal haemolytic crisis may occur

(2) Frequent injections of 3 mg of pilocarpine hydrochloride have been said to give temporary relief

(3) Surprisingly splenectomy is extremely unsuccessful and the death rate is very high It may however reduce the frequency and severity of the haemolytic episodes

(4) Transfusions may be followed by severe haemolytic crises in which the corpuscles destroyed are those of the patient *not* those of the donor This is presumably due to the presence in the infused blood of some haemolytic factor allied to complement

If transfusion does not prove fatal a prolonged remission may follow the haemolytic episode

(5) The only method of treatment that does appear to be of value is the infusion of red corpuscles which have been washed completely free of plasma This should be done sufficiently frequently to maintain the haemoglobin at over 75 per cent

However severe the anaemia *iron should not be given* as it almost invariably invokes a severe haemolytic crisis

Paroxysmal Haemoglobinuria

This is an example of a haemolytic condition due to the presence of abnormal substances in the plasma

It occurs usually in young people more commonly in males after exposure to cold A few minutes or hours after becoming warm there is severe pain in the back headache vomiting severe rigors and sometimes widespread urticaria Cyanosis of the fingers or toes and even gangrene may occur The spleen and liver become slightly enlarged during this time and the urine is extremely dark although not turbid owing to the presence of haemoglobin and sometimes methaemoglobin The urine is clear but in the deposit the ghosts of red corpuscles are seen

The attack is followed by a slight degree of icterus and indeed mild attacks in which icterus is the only sign may occur

Blood

In almost all these patients the Wasserman reaction is positive and even in the cases in which it is not syphilis probably plays an important aetiological role

The blood destruction is due to a haemolysin which unites with the red corpuscles at low temperatures When the temperature is

negative person has developed anti Rh a transfusion of Rh positive blood will cause a severe and possibly fatal haemolytic reaction

In no circumstances should an Rh negative person male or female be given transfusions of Rh positive blood

Once immunization of the mother has occurred it appears to persist indefinitely but there is no known direct relationship between the titre of anti Rh in the mother s blood and the severity of the haemolysis in the infant For this reason prognosis is extremely uncertain

It must be realized that an Rh negative woman who has developed anti Rh can still bear perfectly normal Rh negative children If the father is homozygous Rh positive all the children will inevitably be Rh positive If however he is heterozygous he may beget some Rh negative children The determination of the father s genetic constitution is sometimes serologically possible but sometimes depends upon inference

The severity of the haemolytic disease in the Rh positive offspring of Rh negative mothers is not the same in all matings Thus if the mating is compatible in the A B O grouping the only incompatibility being Rh there is a greater likelihood of the development of the haemolytic disease of the newborn than if there is A B O incompatibility

The explanation is alleged to be that if cells of the incompatible groups escape from the foetus they would be rapidly eliminated before the Rh group had caused immunization A and B being better antigens than Rh In brief therefore the protective action in such a hetero specific pregnancy is due to the competition of antigens the stronger one preventing or diminishing the sensitization

Manifestations of the Haemolytic Disease of the Newborn

(1) The most severe type is that known as *hydrops foetalis* in which there is generalized oedema and signs of very great haemolysis with much extra medullary haemopoiesis These infants are either stillborn or die within a day or two

(2) *Icterus gravis* Jaundice and anaemia are manifest at birth or become so during the first two or three weeks of life There is enlargement of the liver and spleen and even jaundice of the basal nuclei of the brain

(3) *Congenital anaemia* in which pallor develops during the first few weeks of life accompanied by slight jaundice and a varying degree of anaemia These children may die within the first two weeks of life but some recover spontaneously or as the result of treatment

Treatment

The method of prevention of the condition is obvious but it is stated that large doses (300 to 40 mg) of ascorbic acid prevent the haemolysis, even though exhausting exercise is undertaken

Black water Fever

All cases of malaria are accompanied by some degree of haemolysis but, in malignant subtertion the haemolysis may be so intense as to cause haemoglobinuria while at the same time methaemal bumin is present in the blood plasma and may even cause blocking of the kidney tubules

The haemolytic anaemia of black water fever is not entirely or indeed mainly due to the malaria parasite itself but to the presence of circulating haemolysins of uncertain origin

The condition is only mentioned here for the sake of completeness

Haemolytic Disease of the Newborn

The whole series of symptoms that in the past have been known as hydrops foetalis icterus gravis and kernicterus are now included under the one heading — haemolytic disease of the newborn

This disease rarely manifests itself before the third or subsequent pregnancy It is due to the presence of a haemolysin in the maternal blood The formation of this lysin results from immunization by an antigen present in the foetus In the great majority of cases this antigen is the Rhesus factor (Rh) *In other words the foetus* is Rh positive while the mother is Rh negative

There are now known to be a number of sub groups of Rh but their differentiation is a complicated although important procedure which need not be described here The essential facts are that an Rh negative woman who is pregnant with an Rh positive foetus i liable to develop anti Rh although in the first pregnancy of this type the amount of haemolysin produced is not sufficient to cause recog nizable damage to the child Even in a second Rh positive pregnancy the amount of antibody is unlikely to be sufficiently great to cause damage but the third and subsequent Rh positive pregnancies are almost certain to result in one of the manifestations of the haemo lytic disease *of the newborn each Rh positive pregnancy being more* likely to result *in* a stillborn *infant*

An Rh negative woman may develop anti Rh if she has received transfusions *or intramuscular injections* of Rh positive blood and in these circumstances even the first Rh positive pregnancy may result in a diseased or dead child Furthermore if an Rh

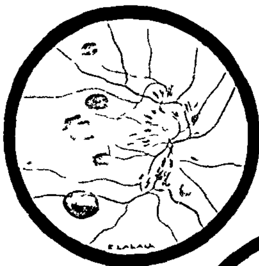


Fig 1 Achrestic anaemia The fundus is a pale greyish pink The *papilla* is pale with slight oedema on the nasal side Striate and flask shape haemor rhages are present and are more numerous than is usual in per nicious anaemia



Fig 2 Osteosclerotic anaemia *Extreme yellowish pallor* of the oedematous retina The papilla is grey pale and oedematous The arteries are almost invisible but the veins are dilated and tortuous Scanty striate haemor rhages are present



Fig 3 Osteosclerotic anaemia Same case as Fig 2 but more advanced with extensive haemorrhages

Blood

The blood picture varies somewhat but the essential features in all types of the haemolytic disease of the newborn are anaemia which may be extremely severe accompanied by the presence in the peripheral blood of large numbers of nucleated red cells of varying degrees of immaturity but all of normoblastic type The leucocytes are usually increased and immature forms mainly myelocytes but some myeloblasts are also present

Treatment

The essential step in treatment is the prevention of the disease For this reason the Rh status as well as the ordinary blood group of all pregnant women should be determined and abnormal antibodies looked for In this way the birth of a child with haemolytic disease may be anticipated and the necessary steps for its immediate post natal treatment be available at the time of delivery

Obviously the unattainable ideal would be the prevention of matings between Rh positive men and Rh negative women

The cases of haemolytic disease of the newborn due to A B O or *other serological incompatibility are so rare as to be of* little importance The possibility of their occurrence could be anticipated by routine grouping and Coombs tests on all pregnant women (p 104)

Treatment of Haemolytic Disease of the Newborn

In mild cases simple repeated transfusions of Rh negative blood have greatly reduced the mortality but severely affected infants die in spite of such treatment

The main cause of death in the first few days of life appears to be hepatic failure and for this reason exsanguination transfusion has been employed for the double purpose of removing free antibodies as well as the child s potentially haemolysable red cells before the liver is overburdened with the products of blood destruction

The technique of exsanguination transfusion in newborn infants is now standardized but requires special experience Here it may suffice to say that about 400 cc of blood are required to replace about 90 per cent of the cells of a 7 lb child

Indications for transfusion As stated above it is essential to anticipate the birth of a child suffering from haemolytic disease of the newborn and not to wait until jaundice or anaemia suggests that treatment is essential because it is then too late to hope for a good result at least in the severe cases

The haematological and serological condition at birth must determine which method of treatment is to be employed

(1) Severe anaemia with reticulocytosis and many erythroblasts bilirubin 4–8 mg per cent but usually only a weakly positive direct Coombs reaction indicates severe disease requiring immediate transfusion preferably exsanguination transfusion

(2) Slight anaemia and moderate reticulocytosis often with few erythroblasts but a strongly and rapidly positive direct Coombs test calls for immediate exsanguination transfusion because in this type of case rapidly progressive jaundice with death on the third or fourth day is liable to occur

(3) No anaemia or erythroblastaemia and only slight reticulocytosis with sudden and rapid direct Coombs reaction and bilirubin less than 2 5 mg per cent is a mild case in which simple transfusion will suffice

(4) No anaemia reticulocytosis or erythroblastaemia bilirubin less than 2 5 mg per cent and a direct Coombs reaction positive after about one minute is a very mild case in which spontaneous recovery is almost certain although simple transfusion may be advisable

These are the brief outlines of treatment but details in the individual case must be left to those with special experience of haematological serology

The practitioner may however be asked whether any other steps can be taken and there is some evidence that induction of labour two or three weeks before term lessens the mortality from the disease especially in the cases in which the maternal blood shows a rising titre Of course it is essential to weigh the dangers of prematurity against those of haemolytic disease and now that exsanguination transfusion is a relatively safe procedure it may be regarded as safer to make preparations for this operation rather than to face the dangers of prematurity

Complications of Haemolytic Disease of the Newborn

It is essential to realize that even if life is preserved whether spontaneously or by treatment unfortunate sequelae may ensue

In cases in which there is jaundice of the basal nuclei of the brain (kernicterus) various types of extra pyramidal syndromes may develop either with or without mental retardation There is however little doubt that the less severe the degree of haemolysis and the earlier treatment is undertaken the le s common are these neurological complications

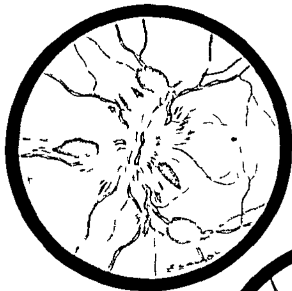


Fig 4 Aplastic anaemia Fundus pallid with a dirty grey tint Papillary and circum papillary oedema is well marked Several patchy haemorrhages and also striate ones with a feathery arrangement



Fig 5 Thrombocytopenic pur pura before splenectomy Pal lor of retina and papilla Vessels pale and slightly tor tuous One large haemorrhage with irregular edges and a clear centre together with fairly numerous petechiae



Fig 6 Thrombocytopenic pur pura a month after splenectomy Same case as Fig 5 The petechiae and larger haemor rhages have almost disappeared

Haemolytic syndromes complicating other diseases are described in the appropriate sections

Coombs Tests

(1) *The indirect anti human globulin test* A delicate method of detecting the presence of Rh antibodies of all kinds depending upon the fact that the antibodies are part of the globulin fraction of human serum There are thus essentially two main stages in the test (i) sensitization of corpuscles by Rh antibody and (ii) agglutination of the sensitized corpuscles by anti globulin serum For example several drops of the serum to be investigated are mixed with cor puscles of the appropriate genotype After incubation and washing one drop of the resuspended corpuscles is added to an equal volume of a dilution of rabbit anti human globulin serum A positive re action which occurs within about a minute indicates the presence of antibody in the tested serum

(2) *The direct anti human globulin test* which reveals the presence of antibody on the red corpuscles It is not specific for Rh but is an important method of detecting as soon as possible after birth whether a child is suffering from haemolytic disease

In newborn infants a positive direct test can reasonably be assumed to be the result of some kind of Rh antibody In children and adults a positive direct Coombs test is found in most cases of acquired haemolytic jaundice on account of the presence of iso anti bodies which are of obscure origin (p 92)

Cirrhosis of the liver is commonly found in infants suffering from icterus gravis shortly after birth and up to the end of the first month It is however supposed that some cases of Wilson s disease (pro gressive lenticular degeneration) in which cirrhosis of the liver is associated with degeneration of the basal nuclei is also a sequel of haemolytic disease

Various bone disorders especially Albright s syndrome in which there are associated endocrine abnormalities have also been shown with some degree of certainty to be late results of icterus gravis

Mental deficiency in some cases is certainly associated with Rh incompatibility but it is uncertain whether this is coincidental Whether such congenital abnormalities such as spina bifida are cor related with similar incompatibility is also uncertain

An important point on which advice is often sought, is whether repeated abortions can be attributed to Rh incompatibility The question has not yet been settled but it is alleged that the incidence of abortions in females with haemolytic disease is lower than the generally expected incidence of 20 per cent Personal experience however suggests that repeated abortions are sometimes due to Rh incompatibility

An important point to bear in mind is that an abortion appears to have a greater immunizing power than a normal pregnancy Hence an Rh negative woman who has had one or two abortions of Rh positive foetuses is very liable to have a first child suffering from haemolytic disease

It is still uncertain whether toxaemia of pregnancy is commoner in Rh incompatible pregnancies but there is a widespread view that this is so (*Anyone requiring further details cannot do better than consult the pamphlet The Rh Blood Groups and their Clinical Effects published by H M Stationery Office*)

Symptomatic Haemolytic Anaemia

This is a rather vague group of cases in which haemolytic anaemia develops as a complication of some other disease such as cirrhosis of the liver syphilis Hodgkin s disease and many other diseases

The cause of the haemolysis in these cases is unknown but it is certainly not always due to the development of a haemolysin Occasionally it appears to be due to hypersplenism (p 116) as is shown by cessation of the haemolytic process after splenectomy In other cases the condition is a true haemolysinic anaemia although the antigen is not known i e it is an example of acquired haemolytic jaundice (p 92)

small amounts in normal plasma and probably plays a great part in the continuous destruction of red corpuscles throughout life In crease of lysolecithin leading to premature senility of the red cor puscles can therefore be the cause of haemolytic anaemia

Complex haemolysins differ from the simple ones inasmuch as they act as sensitizers of the red corpuscles which are then destroyed by complement

The majority of complex haemolysins are of the nature of anti bodies which arise in response to corpuscular or microbic antigens Another type is the cold agglutinin already mentioned in paroxysmal haemoglobinuria Here the corpuscles are sensitized at low tem peratures while complement acts when the temperature rises to 37

Other complex haemolysins exert their effect only when the degree of acidity is suitable

Agglutinins are more commonly found in the blood than are true haemolysins These act directly on the corpuscles without the intervention of complement and there are various types Thus some act only at low temperatures (20) such as the agglutinins known as anti A anti AB and anti B which are normally found in the blood of people of Group B O and A Iso agglutinins only act on corpuscles of the same group

There also exist auto-agglutinins which agglutinate the corpuscles of the patient himself and hetero agglutinins which only agglutinate corpuscles of other blood groups

Cold agglutinins which have only recently been discovered are usually hetero iso and auto-agglutinators but clinically and patho logically the important activity is that of the auto agglutination Thus the spontaneous agglutination of red corpuscles that may occur in virus pneumonia and Raynaud s disease are due to such substances

Agglutinins that act at higher temperatures (37°) are represented by the various Rh anti groups

Some sort of opsonic activity certainly plays an important part in preparing cells for destruction by phagocytosis For example ex perimental injection of doses of haemolytic serum too small to produce any recognizable haemolysis results in greatly increased erythrophagocytosis

(iii) Cellular

Erythrophagocytosis occurs in the cells of the reticulo-endothelial system especially in the spleen where lysolecithin probably acts as a

HAEMOLYSIS IN GENERAL

ALTHOUGH the haemolytic anaemias are relatively uncommon they are sufficiently important to make it worth gaining an insight into the subject of haemolysis even although to a great extent it is of more academic than clinical importance

The main factors leading to haemolysis are corpuscular humoral cellular and splenic although obviously the parts that each of these play overlap

(i) Corpuscular Factors

Changes in the corpuscular membrane whether congenital or acquired lead to premature senility of the corpuscles thus leading to their premature destruction

Such changes in the resistance of corpuscles may be of so delicate a nature as to be undetectable morphologically but more commonly some structural changes indicative of their weakness can be detected

Spherocytosis is the commonest of these abnormalities and contrary to the older belief the spherocyte does not represent a congenital abnormality of the red corpuscle but is an indication of its being in a pre haemolytic and unduly fragile state Thus it is possible to convert normal corpuscles into spherocytes by exposing them to dilute haemolysins

Other abnormalities of the red corpuscles are definitely inherited This applies to such conditions as elliptocytosis sickle cell anaemia and target cell (Cooley s) anaemia

(ii) Humoral Factors

Humoral factors are of great importance These may be simple haemolysins that is to say acting directly on the corpuscles without concomitant action of complement Saponin is an example of one of these direct acting haemolysins Red corpuscles exposed to extreme dilutions *in vitro* become spherical as do the corpuscles of rabbits when small doses of it are injected Various microbic poisons act in a similar way as does snake venom also

An important lytic substance is lysolecithin which is present in

The signs by which the intensity of reaction can be estimated are Reticulocytes often macrocytic in the peripheral blood increased erythropoiesis in the marrow and the presence of nucleated red cells in the peripheral blood

N B Reticulocytosis is a better prognostic sign than is erythro blastaemia which may indicate that the powers of the marrow are approaching exhaustion

Signs indicative of the cause of excessive haemolysis *Corpuscular* Spherocytosis ovalocytosis sickle-cells (drepanocytosis) target cells

Increased fragility of the red corpuscles as shown by testing with hypotonic saline mechanical shaking heat vacuum changes of acidity and exposure to lysolecithin Sometimes it can be shown that the patient s corpuscles are unduly fragile by their diminished survival time when transfused into a normal person

Serological Spontaneous auto agglutination presence of agglu tinins diminished survival time of normal corpuscles transfused into the patient

Spherocytosis will be present but obviously is a phenomenon secondary to the presence of haemolytic substances in the plasma

sort of opsonin and this together with stasis enables the reticulo-endothelial cells to ingest the corpuscles which by this time have become spherocytes

The Results of Excessive Haemolysis

The body can deal with greater amounts of free haemoglobin than the minute quantities normally present but there are limits beyond which it is unable to do so and then the clinical and haematological signs of haemolytic anaemia manifest themselves

Greatly excessive destruction produces an acute fulminating anaemia which may be fatal within a few days The body is unable to deal with the free haemoglobin and its level exceeds the threshold value of the kidney Hence haemoglobinuria occurs and this is often followed by anuria due to blockage of the kidney tubules by acid haematin Death occurs about the fifth day often without any signs of jaundice reticulocytosis or other indications of blood regeneration Larger amounts of haemolysin cause sub acute haemolytic anaemia accompanied by jaundice and spherocytosis which appear quite early while the resistance of the red corpuscles diminishes rapidly Within a few days macrocytic reticulocytes become numerous while there is proliferation of erythroblasts in the marrow and sometimes considerable numbers of nucleated red cells in the peripheral blood The amount of haemoglobin is not above the threshold value of the kidney and it therefore remains in the body and is converted into bilirubin which is excreted by the liver If however as is usual the amount is greater than the liver can deal with there will be bilirubinaemia and an indirect Van den Bergh reaction

Small amounts of haemolysins only produce anaemia and although there is an excess of bilirubin this is excreted so rapidly that there may be no clinical signs of jaundice There is however reticulocytosis in the peripheral blood and intense erythropoietic activity in the marrow

The more important types of haemolytic anaemia have been discussed in this chapter but it may be convenient to summarize signs indicative of excessive haemolysis They are as follows

- Haemoglobinuria
- Haemoglobinaemia
- Indirect Van den Bergh reaction
- Urobilinuria
- Increase of urobilinogen in the faeces
- Increase of plasma iron and less commonly haemosiderinuria

resemblance to thrombocytopenic purpura may be clinically and haematologically very close (Plate II fig 4)

Rarely the initial haemorrhages occur from the gastro intestinal tract or the uterus while very rarely complaint may be made of sudden partial or complete blindness in one eye due to retinal haemorrhage

If the leucocyte mechanism is also affected there will be added to the clinical signs the usual appearances of agranulocytosis i e severe necrotic infection most commonly in the mouth and throat This is accompanied by some degree of pyrexia

When as is usual all the cytopoietic mechanisms of the marrow are affected the term panmyelophthisis is fully justified

It must be said therefore that clinical examination alone will rarely if ever enable a definite diagnosis of aplastic anaemia to be made All it can do is to reveal the presence of a severe progressive anaemia which is not accompanied by enlargement of liver spleen or lymphatic glands and which is never accompanied by sternal tenderness The tourniquet test for capillary resistance is often positive throughout and almost invariably so in the late stages

Blood and Marrow

The state of the peripheral blood does not invariably reflect the condition in the bone marrow Without treatment there is a progressive decrease in the number of red corpuscles which are usually normal in size and show little or no anisocytosis or poikilocytosis The aplasia is rarely if ever complete and therefore there may be some slight evidence of blood regeneration but the reticulocyte count is never high

The haemoglobin falls at the same rate as the red corpuscles and the colour index therefore remains unchanged although cases of dubious nature have been described with a colour index greater than 1 0

Except in the cases of pure red-cell aplasia the leucocytes are reduced in number to about 3 000 although in some cases they may fall in the terminal stages practically to zero At first the reduction is of the neutrophils but ultimately even the lymphocytes diminish Clearly then the condition is not entirely one of marrow aplasia but of general haemopoietic deficiency

The platelets similarly are reduced sooner or later falling below the critical level viz 50 000 per c mm when spontaneous haemorrhages occur The bleeding time is therefore prolonged although the coagulation time remains normal Retraction of the blood clot is poor

CHAPTER X

MYELOPHTHISIC ANAEMIAS (TRUE AND FALSE)

IN this group are included conditions which are more or less rapidly progressive because of inability of the marrow to make good wastage of cells sometimes of only one myeloid type but more commonly of them all

MYELOPHTHISIC ANAEMIA

Aplastic Anaemia

This term is commonly used to denote a condition of anaemia leucopenia and thrombocytopenia due to atrophy of the marrow but as all the myeloid elements are affected it is more accurately called panmyelophthisis

Symptoms

The symptoms that may occur are very variable because the degree of failure of the different cells of the marrow is not always the same Rarely there may be aplasia confined to the red-cell forming mechanism while the leucocytes and platelets remain normal More commonly all the formative tissues of the marrow are affected al though not with equal severity Obviously the symptoms will thus vary from case to case

Usually the onset is insidious sometimes indeed so slow that the haemoglobin attains a very low level before the usual symptoms and signs of anaemia become troublesome Occasionally pallor is the reason for which patients present themselves

In the cases in which the aplasia is confined to the red-cell forming mechanism there are no signs or symptoms other than those directly referable to the reduction of the oxygen-carrying mass that is to say anaemia

In the commoner cases in which the platelet forming mechanism is also affected haemorrhages may be an early sign sometimes even preceding any clinically appreciable anaemia Thus bleeding from the nose and gums may present a difficult problem in differential diagnosis while generalized purpura also leads to difficulties The

borne in mind In connexion with the latter it should be remem bered that thrombocytopenia and anaemia occur very late if at all in cases of genuine granulocytosis

Probably the most difficult and most frequently forgotten disease in this connexion is aleukaemic leukaemia especially aleukaemic *lymphatic* leukaemia In this disease there may be progressive anaemia thrombocytopenia and great reduction in the number of granulocytes with little or no excess of lymphocytes If there is con comitant splenomegaly enlargement of lymphatic glands and sternal tenderness confusion with aplastic anaemia should be impossible In aleukaemic cases however it is not uncommon for most of the ordinary clinical signs of leukaemia to be absent but tenderness of the lower third of the sternum is rarely absent In such cases the only certain method of diagnosis is by marrow puncture which will reveal gross infiltration of the marrow with lymphocytes in all stages of immaturity This is surprising because the lymphocytes in the peri pheral blood are typical mature forms

Causation

It is customary to divide aplastic anaemia into idiopathic and symptomatic types but this serves little purpose and only emphasizes the fact that in some cases the cause cannot be detected

Among the known causes of myeloid aplasia benzol which is widely used in industrial processes is probably the most important Persons suffering from benzol poisoning may develop the typical clinical and haematological signs even after having ceased to be in contact with benzol for months or even years

If careful control is kept on the blood picture of benzol workers it is found that the initial blood change is usually leucopenia and/or thrombocytopenia Later the red corpuscles and haemoglobin fall

It is commonly believed that women especially when pregnant are more susceptible to benzol poisoning than are men and there is some evidence that persons of blood group A are also unduly susceptible

Allied to aplastic anaemia caused by benzol is the similar condition due to trinitrotoluene

Arsenic as used in the treatment of syphilis has occasionally caused aplastic anaemia It is important to realize this possible danger and to attempt to counteract it in the very early stages by injections of B A L although it is still uncertain whether this is of great value in preventing aggravation of the anaemia

Excessive exposure to X rays and radium has long been known as

There are no signs of haemolysis and the icterus index is not raised while the Van den Bergh reaction is negative

There are no changes in the gastric secretion and achlorhydria is no commoner than in the general population

Interesting information can be obtained from an estimation of the level of the serum iron which is distinctly raised presumably as a result of failure to utilize it in the haemopoietic organs Indeed in the early stages of aplastic anaemia this examination may enable a diagnosis to be made

Another investigation which is found to be of value is the so-called *Adrenalin Test* of marrow function Normally injection of adrenalin is followed by an immediate increase in the number of leucocytes after which if the bone marrow is normal slightly immature leucocytes are found in the peripheral blood If the marrow is aplastic the only change that follows the injection of adrenalin is in the number of monocytes

In true aplastic anaemia the condition of the bone marrow is that of diminished cellularity but this cannot always or, indeed often be ascertained with certainty by simple examination of marrow films sections are essential and these may be made either from the clotted marrow fluid or with rather more trouble to the patient from tissue obtained by trephining The sections show greatly diminished size of the individual cellular foci together with a great increase in the number of fat cells This may be so severe that marrow from the parts of the bone that normally are cellular may have the appearance of fatty marrow

Films while not permitting of an accurate estimation of the cellularity of the marrow will nevertheless at least in severe cases reveal a decrease in the number of formative cells and also of mitotic figures

Differential Diagnosis

It is customary to include pernicious anaemia among the diseases from which aplastic anaemia is to be distinguished but there is little reason for this as the clinical and haematological features are entirely different Even so in the past it was not uncommon for pernicious anaemia to terminate in an aplastic stage but whether this was due to the long continuance of the disease or to the treatment with arsenic is unknown

In predominantly haemorrhagic cases one has to think of the various causes of thrombocytopenia while when there are striking infective phenomena the possibility of agranulocytosis has to be

cells is inhibited or there is failure of emigration of fully mature cells

An example of such a condition was seen and still occasionally may be in persons who paint luminous figures on watch dails The continued ingestion of minute amounts of *mesothorium* which is deposited in the bones is followed by the development of a severe anaemia leucopenia and thrombocytopenia not usually accom panied by any signs of regeneration The marrow is however more cellular than normal no doubt in the early stages as a result of con tinuous irritation by the radio-active substance stored in the reticulo-endothelium

The majority of cases in which the haemogram resembles that of myelophthisis while the marrow is fully cellular are not due to any form of poisoning but result from an inhibitory action of the spleen on the marrow

Reactive Myelophthisic Anaemias

Various conditions in which the marrow cavity is diminish d in size or even obliterated can lead to anaemia but as the remaining marrow is more or less healthy it shows signs of reaction which may manifest themselves in the blood by the presence of a varying number of immature red and white cells and sometimes even by the presence of an excess of normal granulocytes

Osteopetrosis

This condition which is better known as marble bone disease or Albers-Schönberg s disease is seen in children usually before the age of ten who manifest signs of generalized disease of the skeleton which may lead to appearances similar to rickets or may cause spontaneous fractures Radiographically there is greatly increased density of the bones with narrowing or in places disappearance of the medullary cavity In milder examples of the disease the bone changes may not become severe until adult life but are always of the same type (fig 7)

There is a distinct hereditary factor in the development of this disease which is equally common in both sexes and consanguinity has been supposed to play a part

The blood picture may be that of a simple normocytic anaemia which sometimes for many years remains slight In other cases either early or after years a different type of blood picture occurs Thus there is anaemia either normochromic or hypochromic with increase of leucocytes some of which are more or less mature poly morphs while others are myelocytes and even some myeloblasts It

occasional causes of aplastic anaemia and many of the pioneer workers died of this disease

Such radio active substances as the paint for luminous watch dials thorotrast and other radio active substances which have been used for diagnosis or treatment can also cause myeloid aplasia

Extensive replacement of the marrow by some foreign tissue such as that of Hodgkin s disease carcinoma etc may cause complete aplasia but this is of course a very different condition from true aplastic anaemia In the early stages of such replacement there is irritation of the bone marrow leading to leuco-erythroblastic anaemia (see p 116)

Many modern drugs among which one should mention the sulphonamides occasionally lead to myeloid aplasia but the danger appears to be very slight

Among the above mentioned causes of aplastic anaemia it must be emphasized that benzol arsenic X rays and radium including other radio active substances are most important because not only may they cause this disease but because workers dealing with them manifest a higher incidence of leukaemia especially of the chronic myeloid form than does the general population

Treatment

Obviously in all the cases in which a recognizable cause is at work the first essential is to remove the patient from such exposure

In the acute cases repeated transfusions may be of some use but the outlook is grave in the extreme In the sub acute and chronic cases repeated transfusions are undoubtedly valuable In the former type of case the disease may become chronic and life may be maintained for a considerable time with carefully matched transfusions as it may also in the primarily chronic cases It has been reported that after long periods of transfusions some degree of marrow activity has been regained but probably complete cure is impossible

In addition it is reasonable although there is little evidence of its efficacy to administer all the substances known to be of value in blood formation e g iron high grade protein amino acids nucleotides etc

Pseudo Myelophthisic Anaemia

This unfortunate term is used to denote those cases in which the state of the blood picture is such as to suggest that the marrow is hypoplastic or even aplastic whereas marrow puncture reveals a fully or excessively cellular marrow in which either maturation of

cases it is impossible to obtain marrow by puncture and suction and then the sternum should be trephined and a small amount of marrow obtained for histological examination

Prognosis

The course of the disease is very long and it is usually only in the late stages that anaemia loss of weight and a tendency to hyper tension becomes manifest Even after this life may be prolonged for a considerable time

Treatment

The only form of treatment that is indicated and that only in the very advanced stages is blood transfusion

In no circumstances must the spleen be removed for it is in virtue of its compensatory haemopoietic activity that life is maintained

Leuco erythroblastic Anaemias

Blood pictures characterized by anaemia erythroblastosis a high leucocyte count and the presence of immature granulocytes may occur in association with a great variety of progressive diseases of the bone or bone marrow For example widespread carcinomatous deposits in the skeleton may cause such a leukaemoid blood picture Sometimes this occurs very soon after metastases have started to develop in the marrow but as a rule it is not until marrow involve ment is extensive that one finds such a blood picture

In a small number of cases of Hodgkin s disease with formation of granulomatous nodules in the marrow a leukaemoid blood picture develops

Similarly in some cases of myelomatosis (p 145) the blood picture bears some resemblance to that of chronic myeloid leukaemia

Hypersplenism

Some reciprocal relationship between the activity of the spleen and that of the bone marrow has long been assumed but only recently has any clearly defined pathological and clinical syndrome due to disorder of this mechanism been recognized The existence of such a correlation is clearly shown by the effects on the bone marrow and blood of removal of the spleen In normal subjects the operation is followed by an immediate increase of leucocytes and platelets while at the same time some abnormalities of the red cor puscles are found These particularly affect the process of de nucleation of the normoblasts For this reason after splenectomy

is common to find normoblasts of various sizes in the peripheral blood and sometimes these are present in very large numbers Such a picture is known as *leuco erythroblastic anaemia* and is in no way characteristic of osteopetrosis as it may occur in association with other pathological conditions which cause narrowing of the medullary cavities

In a few cases the increase of leucocytes is so great as to resemble the blood picture of chronic myeloid leukaemia and this resemblance is even greater because the spleen is also enlarged Such compensatory enlargement of the spleen may occur in any type of chronic marrow destruction

Myelosclerosis

This is a rather vague concept which perhaps includes a variety of pathological conditions which however have in common one factor that of excessive production of fibrous tissue and sometimes bony tissue in the marrow This is accompanied by compensatory development of myelopoietic foci in other organs especially in the spleen

Symptoms

In many cases there is no ill health for many years after the beginning of the pathological process and often it is the large size of the spleen that causes the patient to seek advice The clinical features at this time are of course suggestive of chronic myeloid leukaemia because the spleen may reach the right iliac fossa but there is no tenderness on pressure over the sternum (Plate I figs 2 and 3)

Blood

In some cases the blood picture is the same as that in chronic myeloid leukaemia although as a rule the total number of leucocytes is not as greatly increased Even so ordinary clinical and haematological examination will not enable a differential diagnosis to be made Radiographically in the more long standing cases decrease in the size of the medullary cavities can easily be recognized but in early cases the narrowing may escape notice

Marrow puncture will usually enable a diagnosis to be made partly because of the extreme difficulty in puncturing the bone and partly because little or no marrow juice can be sucked out If any is obtained the cytological features will enable leukaemia to be excluded because one will find a hypoplastic marrow in which for some unknown reason there is an excess of megakaryocytes In some

cases it is impossible to obtain marrow by puncture and suction and then the sternum should be trephined and a small amount of marrow obtained for histological examination

Prognosis

The course of the disease is very long and it is usually only in the late stages that anaemia loss of weight and a tendency to hyper tension becomes manifest Even after this life may be prolonged for a considerable time

Treatment

The only form of treatment that is indicated and that only in the very advanced stages is blood transfusion

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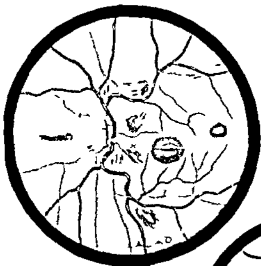


Fig 7 Acute leukaemia Yellowish pallor of the slightly oedematous retina extreme pallor of the papilla Numerous haemorrhages of various sizes into the retina and one in the front of it



Fig 8 Chronic myeloid leukaemia (advanced case) Yellowish pallor of the slightly oedematous retina The papilla is scarcely visible and has diffuse edges Many striate haemorrhages on and near the slightly dilated arteries and other scattered haemorrhages



Fig 9 Malignant reticulosis Pallor of the retina and papilla with numerous haemorrhages

red corpuscles containing basophilic nuclear remnants may be quite numerous in the peripheral blood Traces of this abnormality persist for many years after splenectomy although the changes in the leucocytes and platelets disappear sooner

It appears therefore that the action of the spleen on the marrow is inhibitory rather than stimulating and it is for this reason that the condition of hypersplenism will be briefly discussed here

The effects of the spleen on the elements produced in the marrow may be partial or complete That is to say only the red corpuscles as in acholuric family jaundice (p 84) the granular leucocytes as in primary splenic neutropenia (p 187) the platelets as in essential thrombocytopenia (p 177) or all the marrow functions as in splenic pan haemocytopenia may be involved

The mechanism of the inter relation of the spleen and marrow is not clear Some writers hold that there is a hormonal influence of the former on the latter while others assume that the blood changes are due to either selective destruction of one type of blood or to general destruction of all types in the sinusoids of the spleen

Splenic Pan haemocytopenia

This condition is mentioned in the present chapter because the clinical features and the blood picture may closely resemble or be identical with those of aplastic anaemia Indeed as a rule examination of the peripheral blood will not enable an accurate diagnosis to be made whereas examination of the marrow reveals intense hyperactivity such as of course is never found in aplastic anaemia It would seem therefore that in this condition there is some defect of emigration of all types of blood cells from the marrow This is not however the whole explanation as is shown by the fact that some degree of anisocytosis and poikilocytosis can be found in the blood as these are indications of regeneration This is of course unlike the usual picture of aplastic anaemia

A useful test of spleen and marrow function is the injection of 0 5 c c of one in a thousand adrenalin chloride solution after a complete preliminary study of the peripheral blood A series of characteristic quantitative changes occur in health whereas in some cases of hypersplenism a totally different curve is obtained The test is troublesome inasmuch as it involves blood examination at ten or fifteen minute intervals for two or three hours after the injection It is however important in determining the advisability of splenectomy in such cases but is quite unnecessary as a routine

Splenic pan haemocytopenia occasionally occurs as a congenital

condition or at any rate manifests itself very early in life Usually the severity of the anaemia etc varies spontaneously from time to time and the condition is cured by splenectomy

This is not the type of case in which there is as a rule difficulty in excluding a diagnosis of aplastic anaemia because in the former condition signs of regeneration e g anisocytosis and some degree of reticulocytosis can always be found

An acute form of splenic pan haemocytopenia is also known which firsts manifests itself with much the same clinical features as Lederer s anaemia (p 91) but with no signs of haemolysis The temperature is sufficiently high to suggest the presence of a severe infection while the number of leucocytes is reduced Anaemia rapidly develops the platelets may fall so low that spontaneous haemorrhages occur but reticulocytes are usually more numerous than normal and may indeed be very plentiful

The bone marrow shows an extreme degree of hyperplasia of all the elements but especially of the normoblasts

Diagnosis of this condition is most important because symptomatic treatment in the form of transfusion has only a very transient effect whereas splenectomy is followed by an immediate and persistent release of practically normal cells of all types into the circulation This is of course another feature differentiating this disease from Lederer s anaemia in which one or more transfusions are followed by cure

Secondary Splenic Pan haemocytopenia

The two conditions so far discussed are commonly referred to as being primary This is however nothing more than a confession of ignorance but it is for the time being convenient to retain it and to reserve the term secondary splenic pan haemocytopenia for conditions in which there is definite disease of the spleen associated with a blood picture more or less similar to that of aplastic anaemia and which is cured by removal of the spleen

The spleen is affected in many diseases and when this occurs the functions of the reticulo endothelial cells of the organ tend to become abnormal This is particularly the case when the spleen is greatly enlarged Thus for example in some cases of Gaucher s disease anaemia thrombocytopenia and leucopenia of gradual onset may become so troublesome as to necessitate splenectomy because of the intensity of the hypersplenism Similarly the large spleen of Hodgkin s disease may cause a similar effect It is also possible that the cause of the low white cell count in some cases of aleukaemic

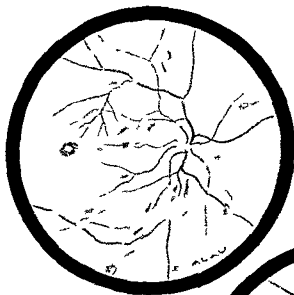


Fig 10 Hodgkin s disease before treatment with nitrogen mus tard Slight pallor of the retina with numerous haemorrhages

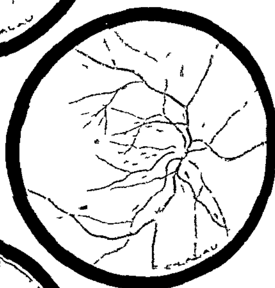


Fig 11 Hodgkin s disease two months after treatment with *nitrogen mustard Most of the* haemorrhages seen in Fig 10 have disappeared but some small punctate haemorrhages have occurred at the posterior pole



Fig 12 *Polycythaemia* The retina has a congested livid appearance The papilla is red with distinct swelling and slight oedema The arteries are dilated and tortuous while the extremely dilated veins present a slaty colour The capillary network is extremely rich and forms arborisations in the papillo macular region

By ou tesy J F Benhamo nd J Fo m

SECTION III

OVERGROWTHS OF HAEMOPOIETIC TISSUE

IN this section will be found descriptions of a rather heterogen eous collection of diseases in which the clinical features and the char acteristic blood changes depend upon the occurrence of excessive proliferation of cells belonging to some part of the haemopoietic tissues It is probable that some of these maladies the leukaemias really do belong to the same pathological and aetiological group while others such as Hodgkin s disease probably do not While our knowledge remains so fragmentary it is convenient to put these perhaps unrelated maladies in one section

leukaemia is not a peculiarity of the disease marrow but is due to hypersplenism

N B There is no direct relationship between the intensity of the hypersplenic action on the marrow and the size of the spleen but absence of splenomegaly is to be regarded as clinical evidence against hypersplenism In almost every case of genuine inhibitory action of the spleen on the marrow at least the lower pole of the organ is palpable

to the disease No changes are clinically detectable in the skin but the blood picture is of course diagnostic Such generalized pruritus is much less common than in Hodgkin s disease (p 9)

Occasionally some skin eruption most commonly herpes is a prodromal sign of any type of leukaemia

Sometimes there is complaint of intermittent malaise which if investigated is found to coincide with slight rises of temperature persisting for a few hours at a time

In more advanced cases there is loss of weight increasing weak ness amenorrhoea and general ill health It must however be emphasized that there is no direct relationship between the clinical condition of these patients and the number of leucocytes in the peripheral blood

A classical symptom is priapism and indeed apart from cases due to local disease this sign is almost pathognomonic of chronic mye loid leukaemia It is however not common and its cause differs in different cases Sometimes it is due to leukaemic infiltration of the corpora cavernosa but perhaps more commonly to the formation of leucocyte thrombi in the corpora cavernosa The condition of the penis is not that of a normal erection inasmuch as the corpora cavernosa are stiff but the corpus spongiosum and the glans are flaccid

Priapism may be spontaneous or may be initiated by sexual excite ment or activity failing to subside when the excitement has passed Established priapism is not accompanied by sexual excitement and it is not abolished bv sexual intercourse

Splenomegaly

An outstanding sign of this disease is enlargement of the spleen which may attain enormous dimensions only exceeded by the spleen of Kalar Azar The increase in size is progressive but, in some cases relatively slow not passing the umbilicus for many months or even several years

In a developed case the lower pole of the spleen extends into the right iliac fossa and the notch is usually easily palpable at about the level of the navel

The organ is firm and not tender to pressure while spontaneous pain is always indicative of some complication The commonest of these is an infarct due to a leucocytic thrombosis leading to destruc tion of a triangular area of the spleen accompanied by inflammation of its capsule When this occurs the inflamed area is tender to pressure and as a rule a friction rub can be heard over it The pain is accompanied by a rise of temperature and some increase of

CHAPTER XI

THE LEUKAEMIAS

PATHOLOGICALLY the leukaemias can be defined as over growths of metaplastic leucopoietic tissue in association with which a variable number of immature and abnormal cells appear in the peripheral blood Further at the present time one can add to this definition by saying that these diseases are inevitably progressive and ultimately fatal disorders

It is unfortunately impossible to approach the subject of the leukaemias from a purely clinical viewpoint It is essential to under stand something of their cytogenesis

It is customary to divide diseases of this type according to the type of leucocyte forming tissue that is predominantly or solely involved Thus there exist leukaemias that are of myeloid lymphatic or mono cytic nature and any one of these may run a chronic or an acute course

Chronic Myeloid Leukaemia

Symptoms

Patients with this disease which is commonest between thirty and sixty may present themselves for a variety of reasons probably the most frequent being progressive enlargement of the abdomen with a sensation of weight especially in the left hypochondrium In many cases however there is nothing more than a complaint of fatigue together with some of the usual symptoms of slight anaemia Often the dyspnoea is surprisingly great in proportion to the reduction of the amount of haemoglobin and this is especially true in the cases in which the spleen is very large Occasionally a case of myeloid leukaemia is revealed by a routine blood examination at a time when there are neither symptoms nor signs of disease

General Condition

Many of the patients look and feel relatively well when first they seek advice but there is an almost invariable complaint of dislike of hot weather This is due to the increased basal metabolic rate

Generalized itching may be the first complaint to call attention

Heart

Tachycardia such as occurs in any anaemia is found but there are no specific clinical features This is surprising because histologically leukaemic cells are often found in considerable numbers between the fibres of the myocardium

Kidneys

Slight enlargement of the kidneys due to leukaemic infiltration is fairly commonly found at post mortem but it is however rare to be able to palpate the kidneys during life not only is the enlargement slight but the enormous spleen renders this impossible

There is persistent increase in the excretion of uric acid associated with a high level of uric acid in the blood This is due to the continuous destruction of innumerable leucocyte nuclei and it, therefore becomes more intense after radiotherapy

Gout is occasionally a complication of untreated chronic myeloid leukaemia and is more likely to occur shortly after radiotherapy which in some patients invariably precipitates an attack

Progress of Symptoms

In untreated cases there is a more or less slow deterioration in the general health with increase in size of the spleen and in the intensity of the anaemia Sooner or later usually within six months of diagnosis the degree of disability is considerable and the subsequent course is often punctuated with short febrile episodes during and after which the splenomegaly increases Such a state of gradual deterioration continues for a variable period but which is on the average from two to three and a half years At the end of this time or even earlier the patient is a complete invalid who sooner or later develops an intercurrent infection such as septic sore throat pneumonia etc or he may present all the signs of acute leukaemia (p 137) death then ensues rapidly

Occasionally in extremely chronic cases short periods of spontaneous remission occur during which the spleen becomes a little smaller the anaemia less severe and the general condition rather better It is however not common for such a spontaneous remission to last more than a month

It is probable that the average duration of life in efficiently treated cases is rather longer than in untreated ones but no convincing statistics are available What is however certain is that efficient treatment greatly delays the time when the patient would become really ill. *Indeed in many cases it is possible to keep the patient in*

malaise which lasts only a few days Occasionally infarction heralds the conversion of a chronic case into an acute one

The size of the spleen varies somewhat from time to time and may diminish greatly as a result of treatment A transient diminution in size can be brought about by sub-cutaneous injection of adrenalin

It may be said that *whenever an enormous spleen is found in* temperate climates it is almost certain that the case is one of chronic myeloid leukaemia This is undoubtedly the outstanding clinical sign of the disease Even so equally great enlargement may occur in old standing cases of myelofibrosis (p 116) and in Gaucher s disease (p 162)

Liver

Slight painless enlargement of the liver is usual in the more advanced cases The organ is smooth painless and moderately firm, but the diffuse leukaemic infiltration which is the cause of the increase in size does not lead to any signs of hepatic failure or of portal obstruction

Skeleton

Complaints of spontaneous pain in the bones is uncommon but occasionally there is dull aching of the sternum the long bones *especially the tibiae and the vertebrae This pain never* attains the severity of that in cases of secondary carcinoma and of myeloma

More commonly these bones are tender on pressure but are not spontaneously painful

The explanation of the pain is undoubtedly the overgrowth of the *marrow pressing on and sometimes slightly eroding the compact* bone but neither tumour formation nor spontaneous fracture ever result

Lymphatic Glands

Lymphadenopathy is not part of the picture of chronic myeloid leukaemia but in the advanced stages slight enlargement of some groups of glands due to leukaemic infiltration may be found

Lungs

There are no specific clinical *changes in the lungs but when the* spleen is extremely large there is some dullness of the percussion note at the left base due to partial collapse of the lower lobe Occasionally a small effusion which is only detectable radiographically occurs in this position

Tuberculosis is a well recognized complication and is liable to run a very rapid broncho-pneumonic course

Spleen The occurrence of infarcts with overlying perisplenitis has already been mentioned and this is occasionally accompanied by perihepatitis When this occurs ascites may develop and herald the end

Spontaneous rupture of a very large spleen rarely occurs but even a slight blow in the splenic region is liable to lead to this inevitably fatal accident

The Skeleton Tumour formation in the bones in chronic myeloid leukaemia is extremely rare but in very chronic cases especially those that have been intensively treated with X rays osteosclerosis may develop This does not produce any local signs but is inevitably followed by further enlargement of the spleen

It is important to remember that a leukaemoid reaction may accompany conditions in which the medullary cavities are progressively and slowly destroyed (p 116)

Blood

The blood picture of a classical case of chronic myeloid leukaemia is pathognomonic even at the time the patient first seeks advice The essential features of the haemogram at this stage are little or no anaemia great increase in the number of leucocytes often up to 500 000 or more per c mm and usually but not invariably a few normoblasts with pyknotic nuclei

The increase in the number of white cells is due entirely to a great excess of elements of the granular series a variable proportion of which are immature i e are younger than those normally set free from the marrow into the blood stream viz metamyelocytes myelocytes premyelocytes and myeloblasts The whole picture is that of extreme over activity of the myeloid tissue because not only are immature cells present but mature polymorphs are present in excessive numbers

The more mature the leucocyte picture as a whole the more chronic is the disease In other words the smaller the percentage of myeloblasts the better is the outlook Indeed the method of assessing the degree of chronicity or acuteness is similar to that employed in assessing the malignancy of any neoplasm

There is however another feature of the leucocyte count which indicates likelihood of an acute exacerbation This is the presence in the blood of mature granular leucocytes and of grossly immature ones (premyelocytes or myeloblasts) with few or no intermediate

relatively good health until a few weeks or even days before d ath which in such circumstances is nearly always due to the disease have become acute

The clinical and haematological changes that may be expected as a result of treatment are described on p 133

Complications

At any time during the course of chronic myeloid leukaemia various complications may arise although these are less common in properly treated cases

Thromboses The thrombi that occur in leukaemia usually consist almost entirely of coagulated leucocytes They may occur almost any where but most commonly in the femoral or intestinal veins Throm bosis of the corpora cavernosa has already been mentioned as an early sign but it may develop at any stage

Leukaemic thrombi differ somewhat from the more usual type inasmuch as they rarely become completely organized

Skin Infiltrations of the skin in chronic myeloid leukaemia are much less common than in the chronic lymphatic form (p 8) and are most liable to develop in the early stages of relapse or towards the end of life In the former circumstances they occur in the dermis as firm miliary nodules often with a violet colour but occasionally haemorrhagic They are most frequent on the trunk and the legs and less commonly on the arms and unlike those of chronic lymphatic leukaemia very rarely on the head and face

Diffuse infiltration of the skin of the whole body probably never occurs in chronic myeloid leukaemia

Haemorrhages The only site in which haemorrhage is at all common in chronic stage of myeloid leukaemia is the retina al though in the acute terminal stage there may be generalized pur pura

The retinal haemorrhages of chronic myeloid leukaemia are almost invariably accompanied by leukaemic infiltration which usually presents a yellow colour with a bright haemorrhagic edge (leukaemic retinitis)

Cerebral haemorrhage is a common cause of death when the disease has passed into the acute stage

Lungs Pleural effusion particularly at the left base is common but more extensive pleural effusions are unusual When they occur they are due to infiltrations of the pleura and the fluid is found to contain immature and abnormal leucocytes often in enormous numbers

Variants in the Haematological Type of Chronic Myeloid Leukaemia

In the great majority of cases the predominant cells in the blood and marrow belong to the neutrophilic series although there is usually a concomitant but moderate excess of eosinophils and basophils

There are however cases in which the predominant cells belong to eosinophil series Sometimes this *eosinophil leukaemia* is accompanied by a great increase of mature eosinophils whereas in other cases the picture is more variegated eosinophil myelocytes also being present The former type is as might be expected more chronic Eosinophil leukaemia may occasionally run an acute course

Basophil leukaemia is an extreme rarity and its main clinical importance lies in the fact that the basophils are almost completely radio resistant and treatment is therefore extremely unsuccessful

It is necessary to mention a rare but confusing haematological state in which there is a very great increase of granular leucocytes sometimes up to 200 000 per c mm all of which are mature polymorphs The clinical condition is that of chronic myeloid leukaemia viz splenic enlargement sternal tenderness etc The blood picture of these cases of *polymorphonuclear leukaemia* gradually sometimes after months sometimes after years becomes converted into that of chronic myeloid leukaemia Cases of this sort run an extremely prolonged course

Occasionally the blood picture of an otherwise typical case of chronic myeloid leukaemia undergoes a temporary or persistent change which is manifested by the presence of large numbers of monocytes When this occurs the total leucocyte count usually rises because these cells emerge in addition to the granular leucocytes It is not clear whether in such cases the monocytosis is due to reaction on the part of the reticulo endothelium or whether it represents a genuinely leukaemic involvement of this tissue

The condition is important because of its resemblance to monocytic leukaemia (p 141) a condition which is usually acute or subacute while this so called Naegeli type of monocytosis in chronic myeloid leukaemia is not always of bad prognostic significance

If the majority of the monocytes are of mature character their presence does not seem to affect the course or duration of the disease In other cases however many of the cells are of the nature of promonocytes or even monoblasts in such circumstances the prognosis is bad because the disease immediately commences to run an acute course Death is however not due to acute monocytic leukaemia but to acute myeloblastic leukaemia or less commonly to acute

forms Such a *hiatus leukaemicus* occurs also in primarily acute myeloid leukaemia and is an extremely grave sign

In the very early stages of chronic myeloid leukaemia the red cor puscles and haemoglobin may be above normal levels and indeed at this time it is impossible to be certain whether the case is one of myeloid leukaemia or of erythroleukaemia

Anaemia which is always normochromic or hypochromic de velops sooner or later but with suitable treatment this may often be deferred for two or three years It does not become at all severe until the leucopoietic overgrowth in the marrow has become so great as to leave inadequate space for the erythropoietic cells

Even before appreciable anaemia develops nucleated red cells usually orthochromatic normoblasts can be found in the peripheral blood presumably as a result of irritation by the proliferating leuco cytes A progressive increase in the number of nucleated red cells in the blood usually heralds the development of the anaemic stage It follows therefore that when nucleated red cells are plentiful in the clinically early stages of the disease anaemia is likely to develop relatively soon In other words this is a bad prognostic sign

In other rarer cases it appears as if the parent cells of both the leucocytic and erythroblastic series are involved in an abnormal proliferative process (erythroleukaemia)

Platelets When a case of chronic myeloid leukaemia is first seen *the platelet count is almost always higher than normal presumably* because of implication of the megakaryocytes in the proliferative process Signs of abnormality in the platelets are often detected some are larger than normal and may even appear to consist of small masses of undivided megakaryocyte cytoplasm while others are extremely small Rarely at this stage portions of megakaryo-cyte nuclei are found in the peripheral blood

Later the platelet count falls ultimately to levels at which spon taneous bleeding occurs and more and more abnormal platelets are present It is at this time that portions of megakaryocyte nuclei either naked or surrounded by a small amount of cytoplasm can be found in the blood

Cases have been described in which the main brunt of the pro liferation appears to fall on the platelet forming mechanism There is then an enormous increase of platelets many or most of which are abnormal in shape and size They are also qualitatively abnormal and haemorrhages dominate the clinical picture of this form of the disease

accessible groups of glands become enlarged while X rays may reveal the presence of masses in the pulmonary hilum although these as a rule do give rise to the symptom of cough It is however only when such a mass is large that any dullness can be detected on percussion between the scapulae

Tenderness on pressure over the lower third of the sternum is not an invariable feature of chronic lymphatic leukaemia but when it is present it can be regarded as conclusive evidence that the marrow is already infiltrated with leukaemic cells That is to say the condition is already a fairly advanced one

The progress of these cases of chronic lymphatic leukaemia is variable some are steadily although slowly progressive until all the lymphatic tissue of the body is involved the spleen becoming enlarged but rarely passing the navel while infiltration of Peyer s patches in the intestine may give rise to intractable diarrhoea which may lead to death from cachexia

In these as in all the chronic varieties of lymphatic leukaemia cutaneous infiltrations are relatively common Occasionally nodular infiltrations in the skin of the face may be a very early sign and may even precede enlargement of superficial glands More commonly however cutaneous infiltrations develop after lymphadenopathy is widespread and severe Although the face is the site of predilection for such infiltrations which may give rise to hideous deformities nodules may occur anywhere on the body surface (see also p 8)

Less commonly there is diffuse infiltration of the skin with lymphocytes leading to generalized erythrodermia with thickening of the skin and complete loss of hair (homme rouge) This dermatological complication is commonest in the cases in which the blood picture is either aleukaemic or sub leukaemic This obviously adds to the difficulty of diagnosis especially as in some of these cases no glandular enlargement can be detected Another relatively common syndrome arises when the initial lymphatic proliferation is in the mediastinum then intractable cough is the usual symptom which brings the patient for advice In the early stages radiography is essential for recognition of the mass but later dullness on percussion between the scapulae and perhaps poor air entry into one or both lungs will enable a diagnosis to be made

The nature of the mass may for a time be difficult or impossible to determine because the symptoms and signs are those of mediastinal tumour and there is no method of determining whether this is a mass of Hodgkin tissue whether it is due to thyoma or is a lymphatic leukaemic infiltration The symptoms and progress usually

leukaemia in which the predominant cells are so immature as to be impossible to classify

In a few cases this Naegeli phenomenon recurs from time to time apparently independently of any change in the clinical condition Its significance in such circumstances is quite unknown

There are no clinical features enabling a distinction to be made between the various cytological types of *chronic myeloid leukaemia* but even so their differentiation is of importance as the prognosis *differs somewhat in the various types*

Chronic Lymphatic Leukaemia

The clinical picture of chronic lymphatic leukaemia is extra ordinarily variable as might be expected from the fact that the patho logical process involves one of the most widespread cellular organs—the lymphatic tissue As a rule this is not all involved at the same time hence the great variety of syndromes that are encountered

Symptoms

The age incidence of chronic lymphatic leukaemia lies between twenty and seventy The condition tends to be more chronic in elderly subjects

Most commonly the first manifestation is enlargement of a small number of lymphatic glands in one region usually on one side of the neck This is not accompanied by any ill health and unless blood examination is made a routine in cases of glandular enlargement the diagnosis may be overlooked for weeks or months because in many cases the progress of the disease is extremely slow Such glandular enlargements present an insoluble problem in *clinical* differential diagnosis although a hint as to the nature of the pathological process can be obtained from palpation of the glands Thus in the early *stages they are never adherent to one another to surrounding struc* tures or to the over lying skin thus differing from tuberculous glands They are firm and painless and do not exhibit the rubbery consistency of Hodgkin s disease Even so it would be a foolish person who attempted to establish a diagnosis on purely clinical examination

At this stage in the great majority of cases the haemogram is already typical of chronic lymphatic leukaemia (p 131) but in a few cases there is no noteworthy lymphocytosis in the blood while the marrow picture is also normal It is particularly in these circum stances that gland puncture is of great diagnostic importance

Within weeks months or occasionally two or three years other

At this time the red corpuscles haemoglobin and platelets are normal presumably because there is no infiltration of the marrow Sooner or later some immature granulocytes and often a few nuc leated red cells are found in the peripheral blood and this should be taken to mean that lymphatic overgrowth is occurring in the marrow From the point of view of prognosis this is not a good sign but it need not be regarded as a particularly grave one

There is no relationship between the height of the lymphocyte count and the severity of the disease and unlike the state of affairs in chronic myeloid leukaemia it is not possible to assess the chroni city or acuteness by the degree of maturity of the lymphocytes In primarily acute cases (p 137) and in a few cases in which the chronic disease is becoming acute the blood contains many lymphoblasts but a chronic lymphatic leukaemia may develop all the clinical signs of acuteness without an increased immaturity of the lympho cyte picture In sub leukaemic cases the blood picture is of the same type but the total leucocyte count is little if at all above normal while the proportion of lymphocytes is high viz up to 90 per cent or even more

Truly aleukaemic cases do occur in which the blood picture is for a time completely normal and it is in these cases that a diagnosis may have to be made by gland puncture or in the cases with an isolated splenomegaly by spleen puncture

A blood picture similar to that just described is not characteristic of chronic lymphatic leukaemia and can only be regarded as being pathognomonic if it persists for a period of at least a few weeks It is important to realize this because an identical picture may occur although of course transiently in some cases of whooping cough and very rarely in miliary tuberculosis

Prognosis

Apart from localization of the lymphatic overgrowth in a vital organ the prognosis of most cases of chronic lymphatic leukaemia is relatively good It is not infrequently that very slowly progressive cases are encountered in which the blood picture and the general clinical features are characteristic but there is little or no deteriora tion of health for five or six years

The Treatment of Chronic Leukaemias

It must be emphasized that the purpose of treatment in these inevitably progressive and fatal disorders is essentially the restora tion of the patient to good health not necessarily the production of a more or less normal blood picture The symptoms and signs of

enable carcinoma of the bronchus to be excluded especially because haemoptysis is rare in chronic lymphatic leukaemia *As it is not* until superficial glands become enlarged that a suspicion of the diagnosis is aroused although of course much earlier than this blood examination is conclusive

Such mediastinal masses are as a rule extremely radio sensitive and for this reason the prognosis in properly treated cases of this syndrome is not worse than in chronic lymphatic leukaemia in general

Other syndromes are relatively uncommon One of the classical although rather rare modes of onset is increase in size of the pharyn geal lymphatic tissue and occasionally great and progressive en largement of one or both tonsils calls attention to the existence of the disease It is important to remember this syndrome because suitable treatment will cause retrogression of the overgrowth whereas tonsillectomy is dangerous because it may convert a chronic case into an acute one

Some of the syndromes of chronic lymphatic leukaemia may be impossible to diagnose during life Occasionally for example there is intense leukaemic infiltration of the intestine with persistent and in tractable diarrhoea but without any other clinical signs of the disease It is only if the blood is examined that a diagnosis can be made otherwise the debilitating effect of the diarrhoea usually proves fatal before there is any glandular enlargement

One syndrome that needs to be mentioned is that in which either on routine examination or because of a complaint of discomfort in the left hypochondrium enlargement of the spleen is found not associated with any other signs of lymphatic overgrowth This occurs particularly in the cases in which there is a sub leukaemic or aleukae mic blood picture Occasionally this syndrome remains practically unchanged for months or even a few years but in other cases the disease becomes acute without development of any other lymphatic overgrowths

Blood Picture

In the early stages of most cases the diagnosis from the haemogram is obvious Thus there is increase in the total number of leucocytes up to 200 000 per c mm but most commonly between 50 000 and 100 000 per c mm The increase is due to a gross excess of small lymphocytes The majority of these look normal under the micro scope but invariably a proportion of the cells are seen to have been ruptured In other words there are signs of their being much more fragile than normal lymphocytes

At this time the red corpuscles haemoglobin and platelets are normal presumably because there is no infiltration of the marrow Sooner or later some immature granulocytes and often a few nucleated red cells are found in the peripheral blood and this should be taken to mean that lymphatic overgrowth is occurring in the marrow From the point of view of prognosis this is not a good sign but it need not be regarded as a particularly grave one

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The Treatment of Chronic Leukaemias

It must be emphasized that the purpose of treatment in these inevitably progressive and fatal disorders is essentially the restoration of the patient to good health not necessarily the production of a more or less normal blood picture The symptoms and signs of

these disorders are in no way related to the high leucocyte count, although variations in this can be used as an indication of the efficacy of treatment

Every method of treating leukaemias gradually loses its efficiency because of the development of resistance of the proliferating leukaemic cells to the therapeutic agent It is reasonable therefore, to commence with the mildest and simplest method of treatment which will result in improvement leaving the more powerful remedies until later In cases of chronic myeloid leukaemia, seen at a time when the general condition is good although there may be a very considerable degree of splenomegaly, one of the most useful therapeutic measures is the administration of *arsenic* by mouth This is best given in the form of Fowler s solution starting with a dose of one minim three times a day and increasing by one minim per dose per day until fifteen minims are being given thrice daily (unless signs of intolerance such as diarrhoea or nausea develop when the maximum dose will have to be much less) The maximum dose should be continued for a week and then the dosage should be decreased by steps similar to those by which it was increased until the patient is taking only five minims three times a day This can be continued as a maintenance dose for weeks months or sometimes two or three years

The effects to be anticipated from this treatment are a decrease in the leucocyte count due mainly to diminution in the number of immature cells viz myelocytes but also some decrease of polymorphs At the same time the red corpuscles and haemoglobin tend to rise to normal while the size of the spleen diminishes and sternal tenderness disappears

Another chemotherapeutic procedure which with care is of great value is administration of urethane This substance which has long been used as a mild narcotic produces changes in the blood and the marrow of chronic myeloid leukaemia very similar to those that are induced by arsenic (although more slowly) and by radiotherapy When the response to urethane is good the blood picture may become completely normal and with a small maintenance dose of the drug be kept so for weeks or months

Urethane although more likely to cause dangerous toxic effects than is arsenic is certainly very valuable but it is essential to examine the blood more frequently during treatment with it, than in cases treated with arsenic *Too great a fall in the number of leucocytes, e g below seven or eight thousand is an indication that there is danger of the development of hypoplasia or even of total aplasia of the marrow*

If the initial treatment of a case of chronic myeloid leukaemia is to be started with urethane it is best to try the effect of 0 5 gramme enteric-coated capsules thrice daily keeping a careful watch on the total and differential leucocyte counts The dose of the drug should never exceed 4 grammes a day and it is rarely if ever necessary to give so much The smaller doses although acting more slowly seem to be just as efficacious

When the blood picture is almost normal the dose of urethane should be reduced to about 0 5 gramme daily and this can be con tinued as a maintenance dose for weeks or months so long as the blood picture remains satisfactory Indeed personal experience suggests that danger is specially likely if urethane is given in a series of courses rather than continuously

An important point in connexion with both arsenic and urethane is that they can be given throughout pregnancy without damage to the foetus Arsenic does not apparently pass the placental barrier and although urethane does so it does not seem to cause any damage Further minute amounts of urethane are found in the milk but these are quite harmless and are not an indication for weaning

Obviously deep X ray treatment is contra indicated during preg nancy because of the possibility of damage to the foetus

Incidentally it may be mentioned that pregnancy does not appear to aggravate the chronic leukaemias and that leukaemic men beget (and leukaemic women bear) perfectly normal children

It is not always easy to decide on the most suitable method of initiating treatment As a general rule it may be said that if the general condition is good the spleen is not very large and the leucocyte count although high is not very immature arsenic is the method of choice even if there is slight hypochromic anaemia If when the patient is first seen there is complaint of severe malaise the spleen extends beyond the navel the leucocyte count is high and the percentage of promyelocytes above five or six urethane is the better method Only if there is really severe impairment of health should the initial procedure be radiotherapy (see below)

When there are either clinical or haematological signs of relapse such as increased splenomegaly return of sternal tenderness in crease of the leucocyte count and/or the development of anaemia it is usually best to start deep X ray treatment rather than to attempt to influence the disease process further by increasing the dose of arsenic

Various methods of using deep X rays are advocated by different authorities but there is little if any difference between the results

obtained by the various methods On the whole the most rapid improvement follows irradiation of the spleen *whereas irradiation* of the skeleton alone although usually ultimately successful is followed by a slower but perhaps more persistent improvement

In expert hands many cases of chronic myeloid leukaemia can be kept *in good health* for three or four or more years by suitably *spaced dosage of X rays but it is essential during the whole of the* time to have frequent blood counts in order to detect the earliest signs of relapse so that irradiation can be started again

The question of arsenical and irradiation treatment being combined is one on which there is divergence of opinion The present *author s view is that a case of chronic myeloid leukaemia first seen* when the spleen is extremely large the leucocyte count very high the sternum extremely tender and the general condition poor is best treated by careful irradiation of the spleen until that organ recedes to or behind the costal margin and the blood picture improves *perhaps even becoming normal When this state of affairs develops* it is often possible to maintain the remission so brought about by administration of a relatively small dose of arsenic e g five or seven minims three times a day given for periods of months or even years

Other methods of treatment are occasionally used but rarely offer *much hope*

It is perhaps surprising that radio active isotopes including radioactive phosphorus have not been found to produce results any better than those following deep X ray treatment There is also the objection that once the radio active isotopes have been injected *it is impossible to stop their action at any desired point*

One of the older methods of treatment was the administration of 5 minims of benzol in olive oil given in capsules This will produce a good remission because of the destructive and inhibitory effect of benzol on blood formation *The objection to the treatment is that very small degrees of over dosage may produce severe anae* mia sometimes of the aplastic type It is therefore better never to employ benzol unless all other remedies have failed to produce a remission and in these circumstances benzol is *occasionally although rarely temporarily successful*

Another substance which although extremely dangerous may produce a remission even when arsenic and X rays have failed is nitrogen mustard (p 160)

Blood transfusion does not play an important part in the treatment of chronic myeloid leukaemia but in cases in which anaemia is severe although the leucocyte picture is not extremely immature

in character blood transfusion may improve the general condition sufficiently to permit of subsequent irradiation treatment

A rather heroic method of inducing a remission in the advanced stages of chronic myeloid leukaemia is exsanguino-transfusion such as has been employed in the treatment of acute leukaemias (p 141)

The treatment of *chronic lymphatic leukaemia* differs a good deal from case to case If there is very slight glandular enlargement and no signs of ill health it is certainly best to employ no treatment at all until deterioration occurs Then if the lymphadenopathy does not increase greatly but the blood picture deteriorates arsenic can be tried (see above) but the effects in chronic lymphatic leukaemia are less satisfactory than in the chronic myeloid form Arsenic may relieve concomitant anaemia but is unlikely to reduce the size of lymphatic overgrowths or the height of the leucocyte count

Urethane exerts relatively little effect on the blood picture and the infiltrations in chronic lymphatic leukaemia and is probably value less in the treatment of this disease

If superficial glandular masses are sufficiently large as to be un sightly local deep X ray treatment will almost always cause their disappearance and the same is true of mediastinal masses In every case however the amount of irradiation given should be the smallest possible as it is easy to induce a state of radio-resistance

Irradiation of the spleen in chronic lymphatic leukaemia may be necessary if as is rarely the case the organ becomes sufficiently large to be uncomfortable but the only effects of irradiation over the spleen will be reduction in the size of the organ and decrease in the number of lymphocytes Irradiation of the spleen is not usually followed by increase of the red corpuscles and haemoglobin When progressive anaemia suggests that extensive lymphatic proliferation is occurring in the marrow further steps must be taken It is best at this stage to perform a marrow puncture in order to confirm that the marrow is being compressed by proliferating lymphocytes but if this cannot be done the presence of such infiltrations can be inferred from the presence of nucleated red cells and some immature granulocytes in the peripheral blood In these circumstances irradiation of the skeleton may be of striking value expecially if the patient be exposed to a generalized X ray bath

Radio isotopes and nitrogen mustard are of little or no value in chronic lymphatic leukaemia

Blood transfusion serves only the same purpose as in chronic myeloid leukaemia (see above)

CHAPTER XII

ACUTE LEUKAEMIAS

THE usual idea of acute leukaemia is that of an acute fulminating disease presenting signs of general infection with localization somewhere usually in the fauces together with severe constitutional disturbance This classical type of acute leukaemia is undoubtedly rare but it presents important diagnostic problems

Acute Leukaemia

Occasionally the first signs of acute and sub acute leukaemia take the form of a localized or generalized haemorrhagic tendency In the former type the bleedings are usually from a mucous membrane commonly of the nose or gums these are due to local leukaemic infiltrations and are not necessarily accompanied by a reduction of platelets In the latter generalized type of bleeding there is extreme decrease of platelets sometimes with localized leukaemic infiltrations Obviously this form of onset is likely to prove rapidly fatal

A peculiar malady probably closely allied to acute lymphatic leukaemia is the so called *Sternberg leuco sarcoma* in which there is a localized mass of leukaemic tissue most commonly in the mediastinum from which tumour cells escape into the circulation either *continuously or intermittently* Later other lymphatic overgrowths may develop and the picture then resembles that of a chronic lymphatic leukaemia with a mediastinal mass which has become acute On the whole the prognosis of leuco sarcoma is rather better than that of acute leukaemia as a whole because the mediastinal mass is often very radio sensitive

It is necessary to mention *chloroma* because although a very rare form of acute leukaemia it is so spectacular The disease is commonest in children and its onset is of the classical variety (p 138) in most cases although sub acute cases do occur The clinical picture is dominated by the development usually early and rapidly of masses in the skeleton especially of the orbits At autopsy the infiltrations are found to be green in colour but it is rarely possible to detect this during life Occasionally however a subcutaneous

deposit may look greenish through the overlying skin and even less commonly retinal infiltrations can be seen to be green

Symptoms

Typically the disease occurs in infants or children although no age is exempt Great care is needed in the diagnosis of *classical acute leukaemia* in older subjects because identical clinical findings may occur in other diseases e g agranulocytosis (p 187)

The onset may be gradual extending over two or three weeks during which the patient is slightly off-colour and perhaps feverish Then usually suddenly there is complaint of sore throat and on examination at this stage the fauces will be seen to be reddened with areas that appear to be almost necrotic The buccal mucous membrane and the gums show a similar condition which may also spread on to the tongue By this time the child is pale and looks extremely ill the temperature is high and of septic type while cervical glands are usually moderately enlarged This lymphadenopathy is not leukaemic but is due to the oral spesis

The lower pole of the spleen may be palpable but in many cases is not while generalized lymphadenopathy is uncommon In children over the age of three tenderness of the lower third of the sternum is usually well marked In younger children owing to the absence of marrow in this position sternal tenderness does not occur

At this stage or even earlier there may be localized or generalized purpura Indeed haemorrhagic phenomena either in the skin or from the mucous membrane may precede all the signs mentioned above The haemorrhages may take the form of petechiae or may be extensive Sometimes there is simple bruising but in may cases careful palpation will reveal the fact that the haemorrhage is occurring into an area of leukaemic infiltration

The retinae must be examined in every case because infiltrations and haemorrhages may occur there earlier than anywhere else Indeed on occasions a clinical diagnosis of acute leukaemia may be made by ophthalmoscopic examination The disease progresses rapidly and inevitably towards a fatal termination which may occur within a week or two or at the most a month or two

Blood

Anaemia usually hypochromic with signs of regeneration such as reticulocytosis and the presence of nucleated red cells is of rapid onset The platelets very soon fall to extremely low numbers and when they are 50 000 or less per c mm haemorrhages inevitably occur

The leucocyte picture has the character of extreme immaturity Thus the great majority of the cells are of the nature of blasts and they are often so undifferentiated that it is impossible to be certain of their exact nature i e whether myeloblasts lymphoblasts or monoblasts *but if forms intermediate between the blasts and mature* granulocytes can be found it is reasonable assumption that one is dealing with acute myeloid leukaemia

Occasionally some or many of the blasts contain scattered azurphil granules or rods in the cytoplasm The presence of these *Auer bodies* is considered as being definite evidence of the myeloid nature of the cells

Another method by which sometimes a distinction between mye loblasts and lymphoblasts is to be made is the *oxydase reaction* Immature cells of the lymphatic series do not contain demonstrable enzymes whereas fairly immature ones of the myeloid series do If *then the reaction is positive the cells are to be regarded as being* myeloblasts but failure of the reaction does not necessarily imply the lymphatic nature of the cells because the most immature blasts are all oxydase-negative For this reason some writers rather pusillanimously speak of stem-cell or haemocytoblastic leukaemias when referring to those in which the exact nature of the cells cannot be determined

As a rule no transitional forms can be found and the presence of an hiatus leukaemicus (p 127) is almost if not entirely pathogno monic

Treatment

Treatment is purely symptomatic The condition of the mouth can to some extent be improved by painting it with N A B paint (0 9 gramme in 20 c c of glycerine and water) Small blood trans fusions may relieve some of the symptoms but has no effect on the course of the disease

The majority of cases of acute leukaemia are much less fulmi nating than the classical type just described indeed they may well be called **sub-acute leukaemia** not because they present a clinical or haematological picture intermediate between chronic leukaemia and classical acute leukaemia but simply because they run a more prolonged course

Symptoms

Sub acute leukaemia is often of insidious onset The period of initial ill health sometimes extends over weeks or even a few months

during which there are no clinical indications of the need for blood examination It is as a rule only when the ordinary symptoms of anaemia manifest themselves that the blood is examined and even then the diagnosis is not necessarily obvious

Many cases of sub-acute leukaemia are afebrile in the initial stages and a diagnosis of aplastic or hypoplastic anaemia is quite commonly made Very careful clinical examination of the whole body surface for haemorrhages and infiltrations of the fauces for infiltrations particularly in the tonsillar region and of the fundus oculi may enable an accurate diagnosis to be made

Blood

The blood picture in sub-acute leukaemias is very variable There is often a general resemblance to the haemogram of classical acute leukaemia That is to say anaemia of regenerative type with a fairly high leucocyte count and many blasts an haitus leukaemicus being well marked In these circumstances there is no particular difficulty about diagnosis

Much more difficult are the cases in which the total leucocyte count is normal or only slightly raised and in which the predominant cells are apparently typical small lymphocytes If an anaemia of a non regenerative type accompanies this picture a diagnosis of aplastic anaemia will be suspected only marrow puncture will enable an accurate diagnosis to be made

The nature of the small lymphocytes is often difficult to determine but there is no doubt that in many cases they are really micromye loblasts or microlymphoblasts which are so condensed as to make it difficult or impossible to detect the presence of necleoli with ordinary methods of staining

Some cases run their whole course with a blood picture of pseudo aplastic type but in some the haemogram becomes frankly leukaemic in the terminal stages

Prognosis

The prognosis in sub acute leukaemia is as bad as in acute leu kaemia but occasionally either spontaneously or as a result of treatment a remission may occur This usually lasts only a few weeks or two or three months but in a minute percentage of cases for a year or two

Treatment

No method of treatment can be relied upon to produce a remission in sub-acute leukaemia Repeated small transfusions will alleviate

the anaemia and sometimes induce a remission More massive transfusions preferably with concomitant exsanguination are even more likely to produce a remission but the procedure is extravagant in its use of blood and the results at the best transient

Folic acid antagonists such as aminopterin also produce a remission in about 20 per cent of cases especially in sub-acute lymphatic leukaemia in children Again the remissions are of short duration and relapse within a few weeks or months is inevitable

A C T H has also been used and produces about the same percentage of remissions as do exsanguino transfusion or aminopterin It may well therefore be that the mode of action of these three therapeutic measures is the same

Symptomatic treatment is also useful in alleviating the patient s distress

Monocytic Leukaemia

The occurrence of monocytosis in the course of chronic myeloid leukaemia has already been mentioned (p 128) In addition to this Naegeli type there is also a condition in which the leukaemic proliferation appears to affect the reticulo-endothelium itself This is true monocytic leukaemia of the Schilling type

Symptoms

The symptoms and signs are similar to those of other acute and sub-acute leukaemias but the onset is quite frequently insidious Infiltrations round teeth or the hypertrophy of the gums is a very common mode of onset the appearances closely resembling those of Vincent s angina

Enlargement of the spleen if present at all is slight but some degree of enlargement of the liver is frequently detectable and this can be regarded as an important point in the clinical recognition of this type of leukaemia

Spontaneous but incomplete remissions are much commoner than in other types of acute and sub acute leukaemia but the general course is essentially the same and the prognosis is invariably fatal

Blood

Progressive anaemia of regenerative type is always present and may become extreme

As a general rule the leucocyte count is relatively low at first the figures rising to as high as 400 000 per c mm in the terminal stages Cases with a very low white cell count also occur and do not run an essentially different course

The majority of the leucocytes are monocytes in various stages of immaturity As the condition progresses more and more primitive monocytes so-called monoblasts increase and ultimately dominate the picture During the remissions however the percentage of monocytes falls and the anaemia improves

The degree of thrombocytopenia is usually less than in other acute leukaemias It is essential to realize that blood examination alone may be misleading because a similar although not identical picture can occur in glandular fever (p 183) and even sometimes persistently in sarcoidosis

Treatment

Therapy is as impotent as in all types of acute leukaemia but transient remissions have followed the use of aminopterin and also exsanguino transfusion

Local treatment of the mouth is rather more difficult than in the other acute leukaemias N A B paint will relieve the condition if there is super added infection with Vincent s organisms but it does not cause improvement of the sloughs The best way of removing these is with a mouthwash consisting of 5 grains of citric acid to 1 oz of water

MYELOMATOSIS

THE leukaemias are regarded by many authorities as being of neoplastic nature but there are many arguments against this view although occasionally as in chloroma the leukaemic masses may take on an infiltrative mode of growth

Myelomatosis is a condition that appears to have some histological relation to the leukaemias but it certainly presents features distinctly more like those of malignant tumours

The exact status of this rather rare disease is still uncertain but as it has been the subject of a good deal of investigation in recent years it deserves fairly detailed consideration here

It is probably fair to say that the one sign of the malady (myelo matosis multiple myeloma or Kahler s disease) that remains in the memory of every practitioner is the presence of Bence Jones protein in the urine There are however many important clinical features of the disease that should be recollected if only because of their importance in the differential diagnosis of various bone disorders

Symptoms

Myelomatosis is extremely rare before the age of forty and the majority of patients are between fifty and seventy men being much more commonly affected than women

Typically the first complaint is of pain usually in the back most commonly in the lumbar region but quite often in the dorsal At this time there may be no other clinical signs except tenderness on pres sure or percussion over the painful areas Fairly often however careful percussion of other bones especially those of the thoracic cage may elicit tenderness

The general health is not impaired at this stage and the diagnosis is quite likely to be overlooked Even if the idea of myelomatosis enters the doctor s mind he may reject it because Bence Jones pro tein is absent from the urine It must be emphasized that this substance is often only intermittently present in the early stages of the disease usually becoming constant when the extent of invasion of the skeleton is much greater

Sooner or later palpable tumours often on the ribs become noticeable while deformities due to softening of the affected bones or even to spontaneous fractures develop The swellings are rarely much larger than a walnut but paper like crepitation can be elicited on pressure Pain becomes agonizing while a number of complications are common Thus anaemia more or less severe causes the usual symptoms paraplegia due to collapse of vertebrae is common haemorrhages may occur spontaneously especially from the gums and chronic bronchitis and emphysema may follow the deformities of the thoracic cage

Tumours are not always confined to the skeleton and it is fairly common to find them in such organs as the tonsil naso-pharynx and testis Indeed in some cases the earliest tumours are extra skeletal It is however probable that these always represent the earlier stages of Kahler s disease but whether the same is true of the rare isolated plasmacytomas that have been described in other organs is uncertain

In most cases there is no enlargement of the spleen liver or lymphatic glands but any or all of these may become enlarged although only moderately so

The radiographic appearances are distinctive although they somewhat resemble those sometimes seen in the reticuloses (p 154) Typically there are punched out areas best seen in the skull and pelvic bones usually without any signs of formation of new bone In the ribs there is more commonly diffuse mottling while in the spine there is rarefaction and later shortening of the whole vertebral column sometimes with disappearance of the intervertebral discs The degree to which the limb bones are affected varies a great deal but it is rare for the upper ends of the humeri and femora to escape while occasionally the whole length of all the bones is affected

The urine in quite 65 per cent of cases contains Bence Jones protein but the excretion of this substance may not be continuous It certainly becomes more frequent and more constant in the later stages but at no time should its absence be regarded as excluding the diagnosis

Bence Jones protein is precipitated at temperatures between 50 and 60 but in some cases at even lower temperatures It passes into solution again at about boiling point Obviously the presence of this substance is less likely to be overlooked if the urine is heated in a test tube in a water bath

Either as a result of concomitant nephritis or of the disease itself albumin may also be present in the urine This is best separated by filtering off the precipitate in the acidified urine at boiling point

A resemblance of the clinical picture to nephritis may be brought about by blocking of renal tubules by casts and a peculiar eosinophilic material while occasionally amyloidosis may occur in the kidney as well as in many or most organs

The Blood

In a few cases there are no alterations in the blood even in the terminal stages of the disease but as a rule anaemia of moderate severity is found When this is severe it may be slightly macrocytic but there is no real resemblance to the blood picture of pernicious anaemia A few normoblasts probably due to irritation of the marrow may be present as may some immature granular leucocytes

Enumeration of the red corpuscles is often very difficult on account of spontaneous clumping and such rouleau formation may make the preparation of films extremely difficult These phenomena are due to the very high level of the plasma globulins which also account for the greatly increased sedimentation rate It is not uncommon to find such figures as 180 *mm* in the first hour of sedimentation Occasionally cold agglutinins are present either alone or associated with the hyperglobulinaemia in the former case the clumping can be avoided by slight heating but quite soon in most cases the plasma globulins also rise

The leucocyte count does not present any constant changes but especially in the advanced stages immature granulocytes may be found Occasionally myeloma cells are present in small numbers and rarely they may be exceedingly numerous If the leucocyte count is very high the condition is sometimes known as *plasma cell leukaemia* which may occur in association with the typical bone tumours or may develop without any obvious skeletal involvement Certainly some of these cases present the histological appearances of leukaemia the infiltrations in the tissues being composed of elements resembling plasma cells

The platelet count does not present any constant changes and spontaneous haemorrhages may occur even when the numbers are normal Poor retraction of the clot may be found especially when there is great hyperprotinaemia although the platelet count is normal

The plasma proteins are almost invariably raised often to 10 gm per cent but occasionally as high as 23 gm The increase is due to the globulins and the albumin globulin ratio is reserved The hyperglobulinaemia can be easily demonstrated by the formol gel reaction which is performed by adding two drops of 40 per cent formalin to

1 c c of serum A positive reaction is shown by the development of a milky gel when the tube has stood for three hours at room temperature N B a positive result is also obtained in kala azar and in trypanosomiasis

The Bone Marrow

Marrow puncture usually reveals the presence of the typical myeloma cells but in the early stages these may not be evenly distributed throughout the skeleton and it may be necessary to puncture several bones in order to demonstrate them Later they can be found in the whole skeleton but are most numerous in the areas in which radiographic changes are most striking Sometimes however myeloma cells can be demonstrated before any radiographic changes are developed

The myeloma cell is commonly regarded as being *sui generis* but there is no doubt that although sometimes very atypical it bears a resemblance to the plasma cell

The marrow is usually very cellular and the myeloma cells may be as low as 3 per cent or as high as 80 per cent the higher figures being found in the more advanced cases

Prognosis

The rare cases in which there is a solitary tumour of the type of a plasmacytoma may be cured by its removal but often the disease spreads in the usual way until the skeleton is extensively involved

In the ordinary case the duration of the disease is about two years but occasionally whether spontaneously or as the result of treatment life is prolonged for several years often with periods of remission and exacerbation

Death may be due to cachexia paraplegia with its usual complications or nephritis with severe nitrogen retention

Treatment

Until recently the only therapeutic measure available was radiotherapy which was sometimes followed by temporary retrogression of the tumours and relief of pain

More recently theoretically very interesting and practically quite useful methods of treatment have been advocated They are based on the biochemical resemblances between Leishmaniasis lymphogranuloma venereum and schistosomiasis in all of which there is hyperproteinaemia and hyperglobulinaemia as there is in most cases of myelomatosis The first three maladies also share the character

of being favourably influenced by antimony compounds For this reason neostibosan and also other substances useful in these three diseases e g stilbamidine and pentamidine have been tried (Tartar emetic is too poisonous)

As a result of these injections peculiar changes occur in the myeloma cells in the marrow basophilic inclusion bodies containing ribose nucleic acid being found in the cytoplasm after about three weeks treatment i e after between 1 800 and 3 500 mg have been given These changes seem to indicate a destructive or at least an inhibitory action of the drugs on myeloma cells which seem to differ from all other marrow elements in being susceptible to this peculiar change

The administration of a low protein diet seems to be essential in obtaining the most intense cellular changes but the amount of protein advocated by American writers seems quite high to the rationed inhabitants of these islands!

There seems to be little doubt that either stilbamidine or pentamidine gives the best results often producing a considerable degree of remission but even more important than this direct result is an indirect one Thus the radio sensitivity of the myelomatous masses is greatly increased and remarkable results are obtained by giving deep X ray treatment after a course of one of these drugs

Cure is still unknown but life may be considerably prolonged while even if not pain and other symptoms are almost always greatly diminished

Urethane given in slightly larger doses than those needed in chronic myeloid leukaemia (p 133) sometimes causes great improvement but there is as yet no means of determining which cases are most likely to respond to a particular type of treatment although there is some evidence that response depends upon which type of globulin is present in excess in the plasma At present treatment has to be more or less experimental

CHAPTER XIV

INCREASED ERYTHROPOIESIS

THE number of red corpuscles may be increased either as a result of reaction to recognizable causes in which oxygen lack always plays a part, or as an idiopathic state The former condition should obviously be known as *erythrocytosis* the latter in conformity with the usage in connexion with the leucocytes as *erythraemia*

ERYTHROCYTOSIS

Erythrocytosis Due to High Altitudes

The reduced oxygen tension of high altitudes leads to an increase in the number of red corpuscles up to 6 or 7 million This may be a purely physiological state and therefore completely symptomless but some people develop a sudden rise of red corpuscles which may lead to headache giddiness and vomiting In the more severe cases pains in the joints are the main complaint and even a slight degree of splenomegaly may be found Restoration to normal occurs within a very few days of descending to sea level

A chronic form of erythrocytosis occurs in residents at very high altitudes particularly in the Andes (Monge s disease) This may also be symptomless but in adults the face and mucous membranes are usually noticeably red the thorax is large and clubbing of the fingers is usual The number of red corpuscles may be as high as 8 or 9 million per c mm

The erythrocytosis that occurs in chronic asphyxia is obviously of the same type

Erythrocytosis of the Newborn

Normally the red corpuscles of the newborn infant are between 5½ and 7 million per c mm The number drops to normal within a week probably mainly as a result of haemolysis but partly because of diminished marrow activity

Erythrocytosis Due to Chemical Agents

All conditions that lead to methaemoglobinaemia are accompanied by moderate erythrocytosis the number of red corpuscles rarely

of being favourably influenced by antimony compounds For this reason neostibosan and also other substances useful in these three diseases e g stilbamidine and pentamidine have been tried (Tartar emetic is too poisonous)

As a result of these injections peculiar changes occur in the myeloma cells in the marrow basophilic inclusion bodies containing ribose nucleic acid being found in the cytoplasm after about three weeks treatment i e after between 1 800 and 3 500 mg have been given These changes seem to indicate a destructive or at least an inhibitory action of the drugs on myeloma cells which seem to differ from all other marrow elements in being susceptible to this peculiar change

The administration of a low protein diet seems to be essential in obtaining the most intense cellular changes but the amount of protein advocated by American writers seems quite high to the rationed inhabitants of these islands!

There seems to be little doubt that either stilbamidine or pentamidine gives the best results often producing a considerable degree of remission but even more important than this direct result is an indirect one Thus the radio sensitivity of the myelomatous masses is greatly increased and remarkable results are obtained by giving deep X ray treatment after a course of one of these drugs

Cure is still unknown but life may be considerably prolonged while even if not pain and other symptoms are almost always greatly diminished

Urethane given in slightly larger doses than those needed in chronic myeloid leukaemia (p 133) sometimes causes great improvement but there is as yet no means of determining which cases are most likely to respond to a particular type of treatment although there is some evidence that response depends upon which type of globulin is present in excess in the plasma At present treatment has to be more or less experimental

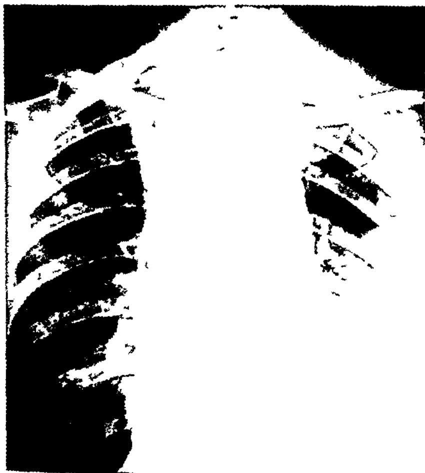


FIG 8 (*a*)—Lymphatic leukaemic infiltration of mediastinum (before X ray treatment)

exceeding 7 million per c mm Poisoning usually industrial with aniline is a typical example Another one of importance is the increase of red corpuscles which can result from long continued administration of large doses of potent liver extract in cases of pernicious anaemia It is probably impossible to raise the number to more than 6 million per c mm by this means and this is not really a pathological condition, it can indeed be regarded as being advantageous because the patients with such high numbers of red corpuscles are much less likely to develop sub acute combined degeneration of the spinal cord

Erythrocytosis in Infections

These are all relatively rare but it is interesting to note that the red corpuscles may be high with a remarkable degree of reticulocytosis in cases of septicaemia due to haemolytic organisms

Tuberculosis of the spleen is an occasional cause of erythrocytosis and may present difficulties in differential diagnosis from true erythraemia (polycythaemia vera) in which splenomegaly may be considerable In the erythrocytosis due to splenic tuberculosis there is however no leucocytosis and this can be regarded as a distinguishing feature

Erythrocytosis in Cardio-vascular Disease

This is well known in association with congenital abnormalities of the heart and also with stenosis of the pulmonary artery The latter condition Ayerza s disease is rare outside South America and is usually of syphilitic origin

Hypertension is often accompanied by a moderate degree of erythrocytosis (see Gaisbock s disease p 151)

Erythrocytosis in Nervous Diseases

This occurs practically only in association with lesions of the mid brain especially in post encephelatics This fact is not of immediate practical significance but is interesting inasmuch as it seems that there is some nervous regulation of erythropoiesis

Erythrocytosis in Association with Gastric and Duodenal Ulcers

In the absence of bleeding a considerable proportion of patients with chronic peptic ulcers have a moderate erythrocytosis e g up to 6 5 million red corpuscles per c mm It is of course quite common to note that these patients have a strikingly red face

commoner in older patients and may indeed be nothing more than an erythrocytosis occurring in association with chronic nephritis and hypertension

Treatment

There are a number of efficacious methods of dealing with erythraemia One of the simplest consists of repeated bleedings each of one pint These can be continued until the red cell count is about five million and then at intervals a pint can be removed in order to keep the count at about this level The objection to this method of treatment is that after months or even years a definite and troublesome iron deficiency manifests itself If this is treated by administration of iron the red cell count rises rapidly Even so this method is still useful in many cases Another method which is rather falling into disrepute is the administration of phenyl hydrazine or acetyl phenyl hydrazine This is a haemolytic agent administration of which can keep the red corpuscles at normal levels

If this method of treatment is chosen it is best to reduce the red corpuscles to about 5½ million per c mm by repeated bleedings and then to keep them at about this level with small doses of one of these drugs Often a normal blood picture and good health can be maintained for years by giving 1½ grains two or three times a week In the cases in which larger doses are required to maintain a normal blood picture there is distinct danger of causing excessive and uncontrollable haemolysis

Generalized irradiation of the skeleton exercises a slow but satisfactory effect on the erythropoietic activity of the marrow in these cases and with care the blood picture can be kept normal for many years by repeated small courses of radiotherapy

The most modern and perhaps the most satisfactory method of treatment is the administration of radio phosphorus This can be given intravenously the initial dose being in the region of 3 millicuries A second dose may be necessary after two or three months but in successful cases a remission of several years may follow this treatment There is indeed considerable evidence that radio phosphorus given by mouth in slightly larger doses is equally successful

The rationale of the treatment is that there is an almost elective affinity between bone and radio phosphorus which is thus deposited in an area from which its radiations exert a continuous but diminishing action on the marrow itself

Strangely enough the heart is usually normal and the blood pressure is little if at all raised

Slight albuminuria is common

Blood

The number of red corpuscles is greatly raised When patients are first seen the number is usually in the region of 9 000 000 per c mm but it may be as high as 14 or 15 million the higher figures being found in the more severe cases

The haemoglobin is raised but not in proportion to the red corpuscles and the colour index is therefore below 1 0 Anisocytosis if present at all is only slight but occasionally a few normoblasts may be seen and the reticulocytes are slightly above normal

Leucocytosis is invariable but rarely great it depends upon increase of mature neutrophils

The platelets are often normal in number but may be increased

The Marrow

The marrow shows a simple hyperplasia of purely normoblastic type with for some unknown reason an increase of megakaryocytes often very considerable

Complications

One of the most important complications is the occurrence of widespread thromboses often cerebral This appears to depend upon the increase of red corpuscles and the liability to thrombosis is decreased or abolished when as a result of treatment the number of red corpuscles falls to normal

Haemorrhages are also common when the red cell count is high These may take the form of haematuria metrorrhagia or cerebral haemorrhage

In long standing untreated cases congestive cardiac failure may occur

An interesting condition which may be regarded as a complication is the development of leukaemia in cases of polycythaemia vera When this occurs it is usually an acute myeloblastic condition but occasionally a case of polycythaemia passes over into one of typical chronic myeloid leukaemia

The so-called Gaisböck s syndrome seems to be a variety of polycythaemia It differs only inasmuch as the blood pressure is greatly raised while splenomegaly is only slight or absent This condition is

CHAPTER XV

THE RETICULOSES

THE concept of the reticulo endothelial system is a relatively recent one and it is essential to realize what is meant by the term Thus when certain electro negative colloids are injected intravenously they are ingested by certain cells in almost all the organs of the body Most of these elements are fixed in the tissues but possess the property of becoming mobile It would in many ways have been simpler to refer to this scattered system of cells as the *macrophage system* thus emphasizing its function rather than its histological characters

The greatest concentration of reticulo endothelial cells is found in the haemopoietic organs both myeloid and lymphatic Thus the basic structure of the bone marrow spleen and lymphadenoid tissue in general is the reticulo endothelium which can be regarded as the great cellular organ of defence against infection by pathogenic agents Indeed there is evidence that it is also the origin of the various forms of humoral defence That is to say to a great extent it is the producer of various types of anti substances In addition to this there is little doubt that the reticulo endothelium is the primordial tissue of all types of blood cells the off spring differing according to the physical and chemical environment in which the particular parent cells lie For example there is little doubt that red cells are produced intravascularly in the bone marrow from the reticulo endothelial cells lining the sinusoids whereas granular leucocytes are produced from the same cells but extravascularly The different fate of the two types of elements thus appears to be due to their different situation Similarly the chemical conditions in lymphatic tissue which are of course totally different from those in the marrow lead to the production of lymphocytes The only cogent argument against this view is that monocytes appear to be produced from the reticulo endothelium everywhere but it may well be that monocytes are no more than reticulo endothelial cells that have become free

Proliferations of reticulo endothelium which are known as reticuloses or reticulo endotheliosis are of several types Thus they may

Di Guglielmo s Disease

It is better to employ the eponymous title of this disease than the one suggested by its discoverer viz erythraemia, because this is liable to lead to confusion with polycythaemia vera which is known by the same name

Di Guglielmo s disease appears to be exactly comparable with leukaemia the difference lying in the fact that the overgrowth is of *primitive red cells not of primitive white cells*

Clinically, the picture closely resembles that of acute leukaemia but anaemia and haemorrhages are of even more rapid onset while gross infection of the throat is extremely uncommon

A diagnosis can only be made by examination of the blood or marrow

Recently sub acute and chronic varieties of Di Guglielmo s have been described but can be regarded as pathological curiosities

Hodgkin s Disease

The exact status of this disease whether infective or neoplastic is *still a matter of discussion but is purely of academic importance* It is quite true that the various more or less complicated classifications of what are known as Hodgkin s disease and atypical Hodgkin s disease are at the present time of little practical significance important though they are in the understanding of the overgrowths of reticulo endothelial tissue while to a much less extent they are of some significance in assessing the prognosis

Symptoms

Hodgkin s disease occurs at all ages but is commonest from late childhood to middle age

Its onset is usually very insidious and often the first complaint is of one or more enlarged glands usually in the neck and for some unknown reason often on the left side

In a few cases the first complaint is of generalized itching which is not associated with any recognizable lesions in the skin Such pruritus may precede enlargement of glands or any other signs of the disease by weeks or months

The rate of increase in size of the affected glands varies greatly from case to case and even from time to time in the same case Furthermore the rate of involvement of other groups of glands is also very variable Sometimes a year or more may elapse after the discovery of the first glandular enlargement before any other lymphadenopathy is detectable whereas in other cases glandular enlargement may become generalized within a few weeks It must be emphasized that in most cases histological examination of one excised gland does not give any indication as to the degree of activity of the pathological process This point will be mentioned again in the section on treatment

The enlarged glands are easily palpable and although they may form quite large masses the individual glands still remain individually palpable while they are not adherent to underlying structures or to the overlying skin

In a few cases the initial glandular enlargement is in the mediastinum and obviously the differential diagnosis will be difficult Even less commonly the initial lymphadenopathy is intra abdominal and *in fairly adipose patients in whom glandular masses are not* palpable the diagnosis may be overlooked for quite a long time It is particularly in these cases that the so-called Pel Ebstein temperature curve is found The chart shows more or less regularly spaced

arise as a reaction to some foreign invader to over activity as for example in storage of abnormal substances or as a neoplastic condition

Reactive Reticuloses

Overgrowth of reticulo endothelial tissue is a characteristic part of the cell response to a great variety of infections mainly of very chronic type For example the epithelioid cells of tuberculosis are proliferating reticulo endothelial elements as are also the foam cells found in foreign body granulomata These conditions are of no direct importance in haematology but a few words must be said about *sarcoidosis*

In most cases the main brunt of the disease is borne by the lungs and differential diagnosis from pulmonary tuberculosis is often difficult In many cases however there is enlargement of superficial glands either in small areas or all over the body and then a suspicion of chronic lymphatic leukaemia is aroused It is common in all the syndromes to which sarcoidosis may give rise to find some degree of enlargement of the spleen which is hard smooth and painless Obviously if such splenomegaly is combined with generalized lymphadenopathy the tentative clinical diagnosis is likely to be leukaemia

Histologically in the relatively few fatal cases that have been examined sarcoid lesions have been found scattered in practically all the tissues including those in which there was no clinical or even macroscopic post mortem evidence In other words the whole of the reticulo endothelium appears to be involved at least in advanced cases It is therefore surprising that no constant blood changes occur Occasionally a moderate eosinophilia or monocytosis has been recorded while mild hypochromic anaemia is usual Even in cases in which there is clinical and histological evidence of the formation of sarcoid nodules in the bone marrow blood changes do not occur Although the extent of sarcoid infiltration of the marrow is as great as that found in some cases of carcinomatosis there is never a leuco erythroblastic response

Sarcoidosis is only of interest in the present connexion because of the occasional associated splenomegaly and because it is one of the conditions in which the lower part of the sternum may be extremely tender on pressure Obviously both these clinical features complicate differential diagnosis

Excision of a gland or if necessary spleen puncture will almost always enable the typical granulomatous tissue to be recognized

sarcoma or reticulo sarcoma It is as yet impossible clearly to define the various syndromes that may arise as a result of true malignancy of reticulo-endothelial tissues

Blood

There is no pathognomonic haemogram in Hodgkin s disease Sometimes or at some stages the haemogram is completely normal while at other times the picture is rather suggestive of an infection

When patients are first seen there is as a rule no blood change Eosinophilia has long been regarded as an invariable concomitant of Hodgkin s disease but it certainly is not so It may occur constantly or intermittently and is particularly common when intra abdominal glands are involved It is however of no diagnostic importance Similarly monocytosis is as variable as is eosinophilia

During periods of active progress of the disease there may be some increase of anaemia with slight reticulocytosis while neutrophils are also moderately increased often with a moderate shift to the left of their nuclear index An increased sedimentation rate is to be regarded as indicative of activity even when no clinical signs are detectable In more advanced stages leucocytosis is usual but not pathognomonic hypochromic anaemia becomes severe but is never of the aplastic type Rarely deposits of Hodgkin tissue in the marrow evoke a leuco-erythroblastic response of the same type as may occur in carcinomatosis

Bone Marrow

In general the bone marrow is normal or is of the type that one would expect from the condition of the peripheral blood e g in a state of normoblastic hyperplasia if there is persistent anaemia It is very rare to find any typical Hodgkin tissue in material obtained by sternal puncture

Diagnosis

Removal of a gland for histological examination is probably the best method of ascertaining that the condition is Hodgkin s disease but in order to avoid this slight surgical intervention gland puncture can be performed It is extremely rare to be unable to find the typical giant-cells of the disease in films made from the material obtained

The lesion in lymphatic glands is of the same type as in all other affected organs Thus essentially there is proliferation of reticulo-endothelial tissue In the early stages this affects mainly the cells of

periods of pyrexia and apyrexia each often lasting two or three weeks Such a type of fever is almost characteristic of Hodgkin s disease and may enable a diagnosis to be made even before super ficial glands are palpable

In about 70 per cent of cases the spleen becomes enlarged although often only the lower pole is palpable On the whole it is true to say that the more advanced the case the larger the spleen which is usually smooth firm and painless although there may be complaints of dis comfort or even of stabbing pain if acute exacerbations occur

A moderate degree of enlargement of the liver develops in many cases

The disease progresses slowly or rapidly In some cases as much as twenty years may pass before the lymphadenopathy becomes generalized and health is impaired whereas in other cases death from cachexia occurs within a year or two

The prognosis is particularly bad in those cases in which pleural effusion occurs This may be haemorrhagic and so resemble the effusion associated with carcinoma of the bronchus or it may be slightly turbid and contain large numbers of endothelial cells or of eosinophils or of both

Many other syndromes have been described as occurring in Hodgkin s disease but only one deserves special mention—the so called Mikulicz syndrome in which there is bilateral enlargement of salivary and lachrymal glands Infiltrations in these sites are usually extremely radio sensitive but differential diagnosis may present difficulties because a similar syndrome may occur in sarcoidosis chronic lymphatic leukaemia and syphilis

Symptoms due to invasion of the skeleton are relatively rare but it is not uncommon to be able to detect radiographic changes De posits commonest in the bony cortex lead either to diffuse or patchy decalcification which may closely resemble metastases of carcinoma Occasionally invasion of the vertebral column is so severe as to give rise to root pains or even to paraplegia

Deposits in the central nervous system are uncommon and occur only in advanced cases They produce the ordinary signs of space occupying lesions in the cranium

Occasionally a case of Hodgkin s disease runs its course very rapidly with severe general disturbances and early onset of cachexia Histologically in these cases the lesions show the ordinary signs of cellular activity such as the presence of many mitotic figures while there is gross variation in the shape size and staining reactions of the component cells Such a condition is then known as Hodgkin

Radiotherapy should be spaced according to the clinical condi tion That is to say when troublesome glandular masses have been reduced to a reasonable size or a mediastinal mass to small propor tions treatment should be stopped and not resumed until after en largement recurs Such intermittent treatment is essential because of the probability of the development of radio resistance if treatment is given continuously

It is difficult to be certain but there is a wide impression that the length of the remission can be increased by administration of arsenic in the same manner as in chronic myeloid leukaemia (p 133)

Sooner or later in every case radio resistance will develop and this usually heralds a fatal termination because by this time in many cases the spleen is very large and there may be ascites and massive lymphadenopathy In spite of the gravity of the condition it is some times possible to produce another remission by intravenous injection of nitrogen mustard in doses of 5 or not more than 10 milligrams on alternate days rarely if ever exceeding 100 milligrams in the whole course of this treatment Occasionally an excellent remission is produced and although rarely some degree of radio-sensitivity may be regained Even so when the time for treatment with nitrogen mustard has arrived the anticipation of life is at the best only a few months

Giant Follicular Lymphoblastoma

It has doubtless become clear that the classification of the over growths inflammatory granulomatous and neoplastic of lymphatic tissue is very incomplete and that many of the pathological condi tions are very closely allied to one another For the present purpose only distinctive syndromes will be mentioned rarer ones only briefly or not at all

The condition known as *follicular lymphoblastoma* or *Brill Sym mer s disease* is worth notice because of its clinical peculiarities and its relatively benign course

The chief pathological characters are enlargement of lymphatic tissue due to great increase in size of the follicles (germ centres) which consist of closely packed lymphoblasts

Symptoms

Enlargement of superficial lymphatic glands usually in the neck is the commonest early complaint At this time the general health is little if at all impaired If the enlargement is only slight medical advice may not be sought for several years because further increase in size is so slight

endothelial type while in the later stages the reticulum increases at the expense of these elements It must be realized that the lesion in one gland may be advanced and almost completely fibrotic while in another it appears to be early and extremely cellular

Similar pictures can be seen in other diseases but in Hodgkin s disease the pathognomonic change is the presence of Sternberg or Dorothy Reed giant cells These are large reticulo endothelial elements usually with more than one nucleus They differ from the giant cells of tuberculosis inasmuch as their nuclei are less enormous and less regular in size Characteristically some of the nuclei have the shape of a hand mirror

It is fairly common to find infiltration of the affected tissues with eosinophils and this may be present even when there is no eosino philia in the blood Again it must be emphasized that the presence or absence of eosinophilia is of little or no diagnostic importance

The lymphadenopathy of Hodgkin s disease presents the ordinary problems of lymphadenopathies in general Thus such conditions as non-caseating tuberculosis metastases of malignant tumours syphilis and chronic lymphatic leukaemia should immediately occur to the physician s mind if these can be excluded the rarer maladies such as sarcoidosis should be thought of

Treatment

It has already been mentioned that in some cases the morbid process remains localized in one group of glands for a very long time whereas in others involvement of other lymphadenoid areas occurs quickly In the former type of case there is no doubt that complete surgical excision of the initial mass may result in cure or at the worst in great prolongation of the time between the onset of the disease and its generalization Although it is impossible to know in which particular case generalization will occur early (or has perhaps already occurred) it must be emphasized that if only one mass of Hodgkin tissue can be found on clinical examination and if radiography fails to reveal any mediastinal mass radical surgery should be tried

In the more common cases which are not seen until there is a more or less generalized enlargement and perhaps even splenomegaly radiotherapy is the treatment of choice As in the case of chronic leukaemia it matters little which particular radiotherapeutic tech nique is employed but an important point to bear in mind is that intensive irradiation of one affected lymphatic area is often followed by decrease in size not only of the treated mass but of other infiltrations

Radiotherapy should be spaced according to the clinical condi tion That is to say when troublesome glandular masses have been reduced to a reasonable size or a mediastinal mass to small propor tions treatment should be stopped and not resumed until after en largement recurs Such intermittent treatment is essential because of the probability of the development of radio resistance if treatment is given continuously

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Symptoms

Enlargement of superficial lymphatic glands usually in the neck is the commonest early complaint At this time the general health is little if at all impaired If the enlargement is only slight medical advice may not be sought for several years because further increase in size is so slight

It is only when other groups of glands become noticeable or when symptoms of anaemia develop that advice is sought By this time careful examination usually reveals other signs of lymphatic over growth particularly enlargement of the spleen which may become very great

In other cases intractable cough due to enlargement of bronchial glands brings the patient to the doctor while less commonly boring pain in one or more bones becomes intolerable

Diagnosis will require gland puncture or even better excision and histological examination Even naked-eye examination may give an almost certain diagnosis because the enlarged follicles are so enormous as to be easily visible As the spleen is not very vascular puncture can quite safely be performed

Treatment

The affected tissues are extremely radio sensitive and relatively small doses of X rays are followed by symptomatic cure Recurrence either locally or in other lymphatic areas in invariable but may not occur for months or even several years Ultimately after many courses of radiotherapy radio resistance may develop

Prognosis

As a rule life is preserved for many years but is punctuated by periods of glandular enlargement and mild ill health Cachexia does not occur until the terminal phases unless as sometimes happens the process becomes frankly sarcomatous

CHAPTER XVI

STORAGE RETICULOSES

IT has already been pointed out (p 154) that the reticulo endo thelium forms a diffuse macrophage system throughout the body Peculiarities of phagocytosis by the cells of the system phagocytosis of unusual material peculiarities in the disposal of ingested material and possibly intra-cellular disturbances of metabolism can give rise to distinctive clinical syndromes But as all these conditions are relatively uncommon they will only be briefly described in this book

Caucher s Disease

All the symptoms and signs of this malady are referable directly or indirectly to the excessive amounts of cerebrosides stored in the reticulo-endothelial system the cells of which become hyperplastic either as a result of irritation or to meet a demand for increased storage capacity

The anomaly is of constitutional origin being distinctly commoner in Jews than in Gentiles but the intensity of the inborn error varies greatly from case to case Thus the disease may first be recognized soon after birth the spleen and liver being extremely large while various signs of nervous disease occur Spleen or liver puncture reveals the presence of the typical Gaucher cells The expectation of life is not more than a few years Much more commonly the disease does not become noticeable until later childhood adolescence or even adult life The symptomatology is more varied in such cases and the expectation of life may be considerable

Spleen

In most cases it is the great splenomegaly that attracts attention The lower pole may extend into the pelvis but neither pain nor tenderness are usual As the early stages of the disorder do not give rise to any symptoms it is usually impossible to ascertain how long the spleen take to reach the large size that is usual when the patients first seek advice If one can draw general conclusions from the few reported cases of familial incidence it is probably usually at least

ten years before the lower pole of the spleen reaches the navel but there is little doubt that progress is slowest in the older patients

The spleen is not as vascular as normal and Gaucher s disease is one of the conditions in which spleen puncture is almost devoid of danger while it is sometimes essential for diagnosis

If the liver is also enlarged severe discomfort and serious complications may result from pressure on such structures as the ureter

Liver

The degree of hepatomegaly is different in different cases but may be very great There are however rarely if ever signs of hepatic failure while jaundice is not part of the usual picture

Lungs

Radiographic changes in the form of small infiltrations may be seen throughout the lung fields in a few cases and this has led to a suspicion of miliary tuberculosis

The very great size of the spleen may cause poor air entry at the left base where as in chronic myeloid leukaemia a small effusion may develop

Lymphatic Glands

In many cases none of the superficial glands are enlarged although it is rare not to find some of the typical Gaucher cells in sections or films Occasionally there is a moderate degree of generalized lymphadenopathy

The Skeleton

It is unusual for the bones to remain normal throughout the course of the disease indeed it is said that radiographic changes are always detectable

Clinically skeletal changes of very moderate severity may accompany the ordinary splenomegalic form of Gaucher s disease Thus there may be some bending of the femora and less commonly of the humeri Radiographically areas of porosis can often be seen while a champagne bottle femur is often regarded as being pathognomonic The radiographic changes are not confined to those areas in which active marrow is normally present any part of the medullary cavities may be affected including the small bones of the hands and feet

Occasionally the skeleton is predominantly affected the spleen and liver showing little clinical sign of involvement. It is in this type of Gaucher s disease that familial incidence is most striking

The Skin

It is commonly supposed that a peculiar yellowish brown colour of the skin is an invariable part of the picture of Gaucher s disease but this is certainly not true of the juvenile examples while the in tensity of the coloration varies even in adults

Much more common than the generalized cutaneous change is the presence of a brownish pinguecula on the outer side of the iris Indeed except in the mainly skeletal type of the malady these always develop sooner or later

As in other chronic splenomegalies ulcers over the malleoli can be common These are preceded by rather dark brownish pigmenta tion and if healing occurs the scars manifest the same pigmentary change

The Blood

It is surprising that a disease that so widely affects the reticulo endothelium should be accompanied by such slight changes in the blood

As a rule slight hypochromic anaemia develops but often only after many years whereas moderate leucopenia due to reduction of neutrophils is constant Later thrombocytopenia may develop and is sometimes sufficiently severe to lead to purpura

The blood changes do not appear to be due to compression or destruction of haemopoietic tissue by Gaucher cells they are the result of an inhibitory action of the spleen on the marrow (hyper splenism) The truth of this is demonstrated by the prompt disap pearance of the anaemia etc after splenectomy

Prognosis

In small infants life is not likely to be prolonged more than a few years In children and adolescents the outlook is quite good but when the malady first manifests itself in adult life the expectation of life may be little decreased It is still not quite clear that splenec tomy prolongs life

Treatment

There is no treatment available for the inborn error of metabolism and the therapy that is adopted will to some extent depend upon

the theory of the disease that pleases the individual doctor Thus if it is assumed that the great reticulo endothelial over growth is due to the picking up of cerebroside from the circulation by reticulo-endothelial cells especially in the spleen it will be reasonable to assume the removal of the organ will inevitably result in the de position of more cerebroside in other areas where as in the skeleton it may be more dangerous If on the other hand it is assumed that the affected reticulo endothelium is hyperplastic because of some abnormality of its own intra cellular metabolism of lipoids it is reasonable to remove the main seat of reticulo endothelial cells—the spleen

Empirically the second view can be accepted because now that a sufficient number of cases have been subjected to splenectomy one can say that removal of the spleen results in improvement Not only is the discomfort from the greatly enlarged organ done away with but there is retrogression of the infiltration in other organs e g the bones

It is reasonable to say that splenectomy should be performed in every case except when the disease manifests itself in very early in fancy and in the few cases in which progress is so slow that no dis comfort is likely to be experienced

Athrocytosis in General

The term athrocytosis is used to indicate those conditions in which there is intra-cellular storage of abnormal substances The concept thus differs somewhat from that of phagocytosis because the latter term is usually taken to imply the ingestion of foreign substances and their subsequent disposal In the case of athrocytosis the stored material may either be the result of phagocytosis or may be formed in the affected cells

An example of athrocytosis is found in the rather rare cases of diabetes with persistent lipoidaemia in which the spleen becomes palpable Spleen puncture or post mortem sections reveal the presence of innumerable lipoid globules in the reticulo endothelial cells Indeed the reticulo-endothelium appears to play a part in both normal and abnormal cholesterol metabolism Thus the pecu liar syndrome known as Niemann Pick disease which occurs only in Jewish infants and which is incompatible with life for more than a year or two is characterized by the presence in most organs of foam cells These contain a cholesterol compound

The Hand Schuller Christian disease which is extremely rare appears to belong in the group of athrocytosis It is especially



Fig 9 —A case of chronic myeloid leukaemia treated with Fowler's solution showing the decrease in size of the spleen after one month's treatment

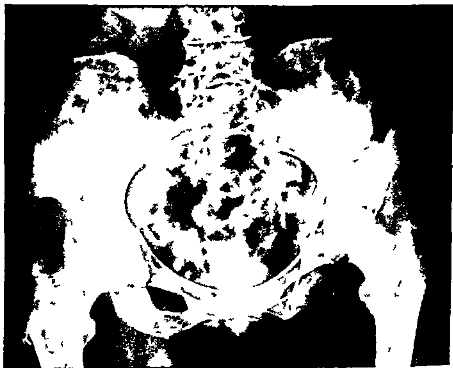


FIG 10 —Pelvis in a case of myelomatosis The typical punched out areas are seen clearly in the ilia and the upper ends of the femora

interesting because its progress is retarded or even arrested by a diet very poor in cholesterol and its compounds

Gargoylism is another example of storage reticulosis in which as in the condition just mentioned bony defects and abnormalities are the characteristic feature

The rarity of diseases of this group is not so great that they can be forgotten in considering the differential diagnosis of cases of spleno megaly especially of those that are not accompanied by noteworthy changes in the blood

SECTION IV

HAEMORRHAGIC DISEASES

THE classification of the diseases in which bleeding occurs either spontaneously or as the result of slight trauma is extremely confused and confusing Not only is this symptom common to a great variety of maladies but there is still not a universally acceptable theory of blood coagulation

In spite of the predominantly practical outlook of the present book it is unavoidable that this chapter should be prefaced by an outline of the more commonly accepted theories of coagulation because without this knowledge it is impossible to gain any comprehension of the group of diseases under consideration Those who wish to pursue the matter cannot do better than to study the masterly review by Macfarlane *

Coagulation of the Blood

Briefly it can be said that coagulation results from the action of thrombin on the fibrinogen present in plasma converting it into insoluble fibrin Thrombin is not a component of circulating blood but is formed from a substance *prothrombin* which is activated by *thromboplastin* (also known as *thrombokinase*) which is set free when blood platelets disintegrate or when tissue cells are damaged

Vitamin K is required for the formation of prothrombin This vitamin which is present in green leaves is also formed in the intestine by the action of bacteria but it is only properly absorbed from the bowel if bile salts are present Hence the haemorrhagic tendency in cases of obstructive jaundice the prothrombin level inevitably falling to low levels

The exact role of *calcium* in coagulation is still uncertain but its importance is indisputable

The problem is further complicated by the presence in normal blood of substances that inhibit coagulation the most important of these anti thrombins are anti-cephalin and heparin

This is the bald outline but it may be convenient to give a succinct

*Macfarlane R G *Junr Clin Path 1948* Vol 1 pp 113 140

account of the story as it is told to-day always remembering that it is likely to be changed time and time again

Coagulation may be started by trauma which leads to admixture of tissue fluid with the blood thus supplying tissue thromboplastin Contact with a rough surface such as an atheromatous plaque can also initiate coagulation because the platelets rupture and set free a lipoid factor which activates a substance thromboplastinogen found in normal blood causing the formation of plasma thromboplastin

From this stage onwards the process of coagulation is the same whether the initiating factor was trauma or contact of the blood with a rough surface Thus thromboplastin reacts with prothrombin which is now regarded as acting as a complex rather than as a single substance It consists of two components known as A B but another substance factor 5 (the last is probably identical with what is called the accelerator factor or Ac globulin or the labile factor) is also needed It seems that the interaction of the prothrombin complex (i e prothrombin A and B) requires the presence of calcium ions and a calcium co-factor for its union with factor 5

Once thrombin is formed it reacts with soluble fibrinogen to form insoluble fibrin possibly through a form known as fibrinogen B

This relatively simple (and possibly partly untrue) story is complicated by the inhibitory factors present in normal blood For instance there is enough anti-cephalin to neutralize the small amounts of thromboplastin that are set free by minor trauma and by moderate destruction of platelets Another important anti thrombin is heparin

Heparin is present in the tissue basophils and in very small amounts in normal blood For therapeutic purposes it is obtained from mammalian lung or liver Its essential effect is as an anti thrombin but it also diminishes the spontaneous agglutinability of platelets

The exact role of the platelets in coagulation is not quite clear but there is no doubt that only a very small number is needed to initiate the process But large numbers are required to ensure proper retraction of the clot Thus thrombocytopenia causes a poor quality clot there are other but less common causes of poor retraction e g decrease of fibrinogen such as occurs in pneumonia (see also p 197)

In connexion with our description of substances that inhibit coagulation it is necessary to mention *dicoumarol* although this differs from anti cephalin and heparin in not being part of the normal anti thrombin mechanism of the body

Dicoumarol was first identified in spoiled sweet clover the eating

of which is known to cause haemorrhagic disease in cattle but it is now prepared synthetically Unlike heparin dicoumarol does not affect the process of clotting *in vitro* and its mode of action although still not quite clear is probably that of preventing the formation of prothrombin B in the liver It also differs inasmuch as it is effective in prolonging the coagulation time when administered by mouth while its effect (decrease of prothrombin) persists for at least twenty four hours and as long as seventy two hours when larger doses are given Then also dicoumarol unlike heparin is not neutralized by protamine sulphate

As heparin and dicoumarol as well as most modifications of the latter substances can be used in the treatment of established thrombosis and as a prophylactic against thrombosis it will be convenient to give some indications of their value and dangers Details must be sought in the relevant literature e g on post operative venous thrombosis and on such conditions as coronary thrombosis

Obviously such potent agents are not devoid of danger and some of the methods of assessing their effects must be mentioned

Coagulation Time

It is clear from what has already been said that the time blood takes to clot depends upon a large number of factors and the determination of the clotting time is therefore only a rather rough guide Certainly in any case under treatment with anti-coagulants prolongation of the clotting time must be looked for and if found investigated further Essentially it may be said that prolongation may be due to lack of calcium fibrinogen prothrombin or vitamin K The disorders in which these various factors play a part will be discussed later in the present section

In connexion with treatment with dicoumarol and similar substances the determination of the *prothrombin time* is more important than that of the simple coagulation time Obviously the ideal method of estimation of prothrombin would be the determination of the amount of thrombin that is formed This is far too time consuming for ordinary purposes and simpler but indirect methods are used The general principle that governs the many techniques that have been suggested is that a mixture is made of optimal quantities of all the factors needed for coagulation except prothrombin the coagulation time of the mixture is then inversely proportional to the amount of prothrombin present in the test plasma No more need be said here except that checking the prothrombin time is a very expert job

Anti-coagulants in Treatment

It may be said that heparin can safely be used (of course in proper dosage) in all cases of thrombosis there are no concomitant diseases that need to be considered as contra indications Further the safety of heparin is increased by the possibility of rapidly stopping its anti coagulant action by intravenous injection of 10 c c of 1 per cent protamine sulphate

Dicoumarol on the other hand is a potentially dangerous drug which should never be given if there is any kind of liver disease (or even strain on the liver as in pregnancy) It should obviously not be used at the same time as other drugs that have an anti thrombin effect e g salicylates quinine

Briefly it may be said than when an immediate prolongation of coagulation time is required intravenously administered heparin is essential although its effect will have almost disappeared after three or four hours This transience can be avoided with some trouble by slow continuous intravenous infusion

Heparin for intramuscular injection has recently become available but is not completely satisfactory

Dicoumarol can be given by mouth and has a prolonged effect It has however the disadvantage of being cumulative while its effect is often very difficult to stop

It is usual to give doses of approximately the following sizes — 300 mgm the first day and 100 to 200 mgm on subsequent days until the prothrombin in the blood reaches about 30 to 40 per cent of normal This level is then maintained by carefully considered daily dosage

Haemorrhages due to dicoumarol can often be controlled by in fusions of really fresh blood and sometimes by intravenous in jection of synthetic vitamin K in doses of 60 to 100 mgm every two hours for five or six doses It has been stated that nicotinamide (100 to 200 mgm daily) together with large doses of ascorbic acid are also useful In any case in which haemorrhages occur all these methods should be tried concomitantly

A recently introduced preparation which goes under the trade name of Tromexan has the same effects as dicoumarol while it is much less dangerous The course of treatment is approximately as follows —4 tablets on the first day 3 or 4 on the second and 1½ to 2 on subsequent days the aim being to reduce the prothrombin level to 20 or 30 per cent of normal The contra indications and the treat ment of over dosage are the same as for dicoumarol

CHAPTER XVII

HAEMORRHAGIC DISEASES

THE mechanisms by which the excessive bleeding is brought about are numerous and in almost all the haemorrhagic diseases more than one factor plays a part It may simplify the subject if a tentative classification is given although not all the disorders mentioned in it will be discussed It is however necessary to know even if vaguely of their existence in order to consider them in differential diagnosis

(A) ESSENTIAL HAEMORRHAGIC DISEASES

I HEREDITARY AND CONGENITAL HAEMORRHAGIC CONDITIONS

1 Disturbances of coagulation
- (a) Haemophilia (in which the essential abnormality is disturbance in the formation of thromboplastin)
- (b) Congenital fibrinopenia
- (c) Congenital hypo prothrombinaemia
- (d) Parahaemophilia (deficiency of Factor 5)
- (e) Congenital deficiency or absence of thromboplastin
- (f) Hereditary haemorrhagic thrombasthenia (Glanzmann s disease)

2 Disorders of the platelets
- (a) Hereditary thrombopathy
- (b) Essential thrombocytopenia (Werlhof s disease)

N B —Heredity does not play an obvious part in all the above diseases

3 Vascular Factor
- (a) Familial purpura simplex
- (b) Inherited vascular abnormalities (the only important one for our present purpose is hereditary telangectiasis)

II AVITAMINOSIS

1 Vitamin C deficiency (leading to vascular disturbance)
  (a) Scurvy
  (b) Barlow s disease
2 Deficiency of vitamin K (prolongation of coagulation because of deficiency of thromboplastinogen)
3 Deficiency of vitamin P (?)

III ENDOCRINE DISORDERS

1 Puberty
2 Menstrual
3 Menopause
4 Cushing s syndrome
5 Thyrotoxicosis

IV CHEMICAL CAUSES

1 Drugs such as sedormid (destruction of platelets in the blood) benzol (damage to megakaryocytes in marrow) nitrogen mustard (damage to vascular endothelium and to marrow cells)
2 Animal poisons e g snake venom
3 Vegetable poisons e g saponin

V PHYSICAL AGENTS (leading to vascular damage)

1 Temperature
  (a) Cold
  (b) Burning (often associated with secondary liver damage and hypothrombinaemia)
2 Irradiation
  (a) Ultra violet
  (b) X rays and radium
3 Gravity

VI VASCULAR AND NEURO VASCULAR DISTURBANCES

1 Allergic purpura
  (a) Schonlein s disease
  (b) Henoch s purpura
2 Purpura fulminans
3 Various skin diseases
4 Malnutrition
5 Psychogenic

(B) SYMPTOMATIC HAEMORRHAGIC CONDITIONS

I MARROW DAMAGE

1 Leukaemia
2 *Panmyelophthisis*
3 Hypersplenism etc

II INFECTIVE DISEASES *(producing haemorrhages mainly by vascular damage)*

1 Acute exanthemata especially typhus haemorrhagic measles and haemorrhagic scarlatina
2 Septic infection
  (a) Septicaemia
  (b) Friedrichsen Waterhouse syndrome
  (c) Meningococcal bacteraemia with generalized purpura and bilateral suprarenal haemorrhages

III ALLERGIC CONDITIONS (leading both to vascular damage and disturbances of coagulation)

IV *VASCULAR DISEASES PURPURA*

1 Senile purpura
2 Haemorrhages associated with hypertension

V HYPOTHROMBINAEMIA ASSOCIATED WITH

1 Liver damage
2 Defective intestinal absorption e g Coeliac disease sprue etc (deficiency of vitamin K)

The great majority of conditions in which bleeding is a predominant symptom are included in the above classification but it must be admitted that a certain amount of overlap has been unavoidable

Haemophilia

This is probably the best known of all the haemorrhagic diseases and the term bleeder has become common as a lay diagnosis Of course only a small proportion of bleeders are haemophilic and exact diagnosis of the cause of excessive bleeding is of great practical importance

Symptoms

Although haemophilia is an inherited disease the tendency to bleeding is not obvious at birth e g there is no excessive loss of blood from the umbilical cord

A second and very important point is that the intensity of the in herited peculiarity is not equally great in all cases and that perhaps for this reason the time of onset of the earliest symptoms is variable Usually the tendency is first noticed between the ages of two and four when bruising after small bumps and falls is extensive In a smaller proportion of cases the bleeding tendency is not observed until between the age of ten and the onset of puberty It is almost if not quite safe to say that a haemorrhagic condition that first be comes manifest after puberty is not haemophilia but is likely to be an acquired malady

The later *in life the first symptoms appear the slighter is the* abnormality—and the better the prognosis

Haemophilia is a disease of males which can at least theoretically occur in females (see below)

Another feature is that the haemorrhages are never spontaneous an injury often of the very slightest character is required to initiate the loss of blood A scratch may start a haemorrhage that is so per sistent as to become dangerous to life while tooth extraction is a very dangerous operation Even the normal eruption of the first (or more commonly the second) dentition may cause fatal haemorr hage

Epistaxis is common and melaena or haematuria occurs at some time in about half the cases But one of the constant features is recurrent bleeding into one or more joints especially the knees ankles and elbows

The onset of haemarthrosis is usually sudden with signs suggestive of infection Thus the joint becomes swollen reddened and hot while the peri articular tissues are also swollen and doughty Fever up to 102 is also usual The blood may be rapidly absorbed leaving the joint little if at all damaged but repeated haemarthroses lead to gross changes in the articular surfaces and ultimately to deformi ties and ankylosis

True purpura never occurs but large subcutaneous and intra muscular haemorrhages are frequent

In spite of the inherited nature of the abnormality the haemorr hagic tendency varies from time to time there may be weeks or months during which the patients notice that they are little more liable to bleed than are their normal friends while at other times

(B) SYMPTOMATIC HAEMORRHAGIC CONDITIONS

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2 Panmyelophthisis
3 Hypersplenism etc

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Haemophilia

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the amount of prothrombin consumed is extremely small but this also varies with the phase of the disorder being greatest during remissions

The clotting time of recalcified plasma is of diagnostic importance even during remissions Thus if the platelets are removed from haemophilic plasma by very rapid centrifugation the coagulation time of the recalcified platelet free plasma is much longer than that of platelet-containing oxalated plasma Similar treatment of normal plasma reveal only minute differences between platelet free and platelet-containing plasmas Unlike the other tests this one is of diagnostic value even during remissions

In haemophilia the bleeding time paradoxical as it seems is normal whether the coagulation time be prolonged or not

Clot retraction is normal

Diagnosis

When a typical family history is obtained in the case of a male who bleeds easily the diagnosis of haemophilia is fairly obvious but confirmatory tests are of course needed

Some difficulty may arise in connexion with the condition known as *fibrinogenopenia* which may be a congenital abnormality Here however the blood will not coagulate when tissue thromboplastin is added to it whereas haemophilia clotting occurs because the main defect in the latter malady is deficiency of thromboplastinogen

Acquired fibrinogenopenia is not likely to cause confusion because it occurs as a complication of some other serious malady such as for example advanced biliary cirrhosis carcinoma etc

Treatment

Bleeding must be dealt with immediately not awaiting spontaneous haemostasis If the site of the haemorrhage is accessible the clot should be washed away and then one of the following should be applied thrombin (e g the Thrombin Topical of Parke Davis & Co) 1 in 10 000 dilution of Russell viper venom (Stypven of Burroughs Wellcome & Co) fibrin foam soaked in thrombin or mixtures of plasma and thrombin

When these measures fail or if the site of the bleeding is not accessible blood transfusion preferably with fresh blood will almost invariably stop the haemorrhage

Blood transfusion is also the best prophylactic against bleeding if any surgical operation is to be undertaken

The haemostatic sera that were advocated and used extensively appear to be quite inert

bleeding occurs after the least trauma There is little doubt that many haemophilics are able to anticipate the onset of a bleeding phase by their feeling of malaise

In most of the patients who survive to adult life the tendency becomes less noticeable as the years go by and the periods of quiescence usually also become longer

N B —*The capillary resistance test is never positive in haemophilia*

Inheritance

Haemophilia is inherited as a sex linked recessive character It is confined to males but is transmitted by females Thus a haemophilic man cannot transmit the abnormality to his sons but only to the sons borne by his daughters Of these grand daughters about half will be normal (i e not transmitters of haemophilia) while half will carry the abnormality

N B —The sons of a haemophilic father are normal The offspring of the mating of a haemophilic male with a female carrier would result in the birth of haemophilic children both male and female

It has already been mentioned that the intensity of the bleeding tendency varies from case to case but it is also true that there are families in which a severe defect is transmitted and others in which only a mild one is inherited

In the case of many of the apparently normal daughters of haemophilic men there is a distinct although slight prolongation of the coagulation time and there may even be a slight tendency to bleeding e g moderate menorrhagia

Blood

There are no pathognomonic changes in the haemogram Ordinary post haemorrhagic anaemia develops after bleeding but this rapidly recovers

The striking change is prolongation of the coagulation time sometimes to several hours Important though this finding is it must clearly be understood that during remissions the coagulation time may be normal or nearly so Obviously then if faced with a history of bleeding and a proper family history the occasional finding of a normal coagulation time must not be regarded as excluding the diagnosis

A useful if rather complicated test is the measurement of prothrombin consumption The principle is the determination of the prothrombin time of serum at intervals after coagulation has occurred thus gaining an insight into the amount of prothrombin consumed in reacting with plasma thromboplastin In haemophilia

A profuse crop of haemorrhages develops distal to the cuff Even during periods of clinical remission the capillary resistance is usually less than normal

The disease has much less commonly an acute onset starting with pyrexia and more or less generalized purpura Even less commonly the bleeding is confined to one mucous membrane e g the uterus and the diagnosis in such cases is likely to be overlooked

In the acute cases even the slightest trauma such as percussion may produce purpuric patches

Blood

A striking feature is the diminution in the number of platelets which during haemorrhagic crises fall below the so-called critical level viz 50 000 per c mm Not only are the platelets quantitatively reduced they also show structural abnormalities such as the presence of giant forms absence of granules and failure to agglutinate while films are being made

There is no very characteristic change in the morphological blood picture but severe or persistent haemorrhagic episodes leads to a simple hypochromic anaemia Leucocytosis usually accompanies the bleeding

During remissions the platelets may rise to very nearly normal numbers but more often rise to a level a little above the critical one Even in the most complete spontaneous remissions abnormal plate lets can be found

The condition of the *bone marrow* varies a good deal from case to case and is important in assessing the prognosis

1 Megakaryocytes may be normal but fail to become completely mature and give rise to platelets Such a failure of maturation may be associated with hypersplenism and obviously in such cases one would expect splenectomy to effect a cure
2 Megakaryocytes may be extremely scanty as a result of specific hypoplasia of these elements This is probably rarely if ever the mechanism at work in essential thrombocytopenia although it is common in the thrombocytopenias due to some toxic cause (p 172)
3 Failure of maturation of megakaryocytes due to some unknown allergic factor has been postulated Thus it has been stated that if the eosinophil count in the marrow is high anti allergic treatment and blood transfusion will result in cure whereas cases with a normal eosinophil count should be treated by splenectomy

Many methods of treating the malady itself have been suggested but apart from prophylactic measures nothing of real value has emerged The patients need to be guarded against injury and sepsis which is undoubtedly a potent cause of exacerbations

Hereditary Haemorrhagic Thrombasthenia

This is a rare disease but is worthy of mention because although inherited it occurs in both males and females

The symptoms are similar to those of essential thrombocytopenia which is rarely if ever hereditary e g excessive bleeding bruising from small injuries and purpura

The coagulation time is normal but the bleeding time is prolonged The platelets count is approximately normal but the individual platelets show abnormalities in shape and size The platelets are also functionally defective as is shown by the poor clot retraction

No treatment affects the disease and splenectomy is certainly useless The malady is transmissible from generation to generation but unaffected members can safely have children

The mortality is said to be high but in a number of cases there has been spontaneous improvement with advancing age

Essential Thrombocytopenia (Werlhof s Disease)

This is the best known and commonest type of purpura and as in many cases treatment is unsuccessful proper diagnosis is extremely important

Symptoms

The majority of cases are of a chronic type often running a course punctuated by remissions and relapses although a continuous form of the disease also occurs

The onset is usually in childhood and is manifested either by unduly excessive bruising after slight injuries or by what appears to be spontaneous purpura Not uncommonly epistaxis or bleeding from some other mucous membrane ushers in the disease

In the early stages the spleen is not palpable but in the chronic persistent cases or after severe relapses in the intermittent type of the disease the lower pole of the spleen usually becomes palpable Tenderness of the lower third of the sternum is never very intense but is present during periods of active regeneration

Chronic ulcers over the malleoli occur in a small proportion in long standing cases

The most striking clinical feature of the disease is the positive tourniquet test This shows a greatly decreased capillary resistance

Large doses of vitamin C given intravenously may evoke a re mission but probably never lead to a cure

Haemorrhagic Hereditary Telangiectasis

This is a rare condition which is characterized by haemorrhages which are due to the development of multiple telangiectases It appears to be due to a hereditary malformation of capillaries It affects both sexes equally and is transmissible as a dominant In most cases the disease first manifests itself by epistaxis but often not until adult life On examination small dilated capillaries can be seen As the years go by small stellate vessels develop on and around the lips tongue and on other mucous membranes even in cluding the gastro intestinal tract

No treatment apart from cauterization has any effect and although Rutin has been advocated it is very doubtful whether it is of any use even in gastro intestinal bleeding

Symptomatic Thrombocytopenia

Reduction in the number of platelets and purpura may occur in a great variety of diseases either as a result of bone marrow failure partial or complete or of hypersplenism In this group (see IV p 172) is included the thrombocytopenia due to sedormid which is a mild hypnotic This is a particularly interesting and important condition because it appears that the platelets are destroyed in the peripheral circulation and any changes in the megakaryocytes are secondary being essentially regenerative in nature

There is reason to suppose that such sedormid purpura is due to sensitization and that persons who take the drug intermittently are more likely to develop purpura than those who are in the habit of taking it continuously

There are no pathognomonic features of sedormid purpura but sudden onset in adult life which is uncommon in essential thrombocytopenia should arouse suspicion of a chemical cause

There is no treatment apart from stopping the drug The haemorr hages are then rapidly absorbed while large numbers of young but normal platelets are poured into the circulation Even the slightest dose of the drug will cause a severe relapse

Purpura Due to Vascular Disturbances (see VI p 172)

An outstanding example of this is *Schonlein s disease* which is sometimes known as purpura rheumatica because the condition is characterized by peri articular swellings with pain and tenderness

N B —In these cases there is no correlation between the eosinophil counts in the blood and in the marrow

The genesis of the haemorrhages is still not completely clear but it is obvious from the result of the capillary resistance test that there is an increased permeability of the vascular walls It must therefore be assumed that there are three possible factors viz defective production of platelets in the marrow damaged capillary endothelium and perhaps *excessive destruction of platelets in the reticulo endothelium* mainly of the spleen

Treatment

A definite but uncertain proportion of the cases recover spontaneously sometimes after severe relapse This of course makes assessment of the value of treatment rather difficult

In acute cases splenectomy is fatal but dangerous haemorrhage *can almost always be controlled by blood transfusion* There is however little doubt that really fresh blood or even arm to-arm transfusion is preferable to stored blood because the latter contains very few if any platelets

It has been claimed that small transfusions at intervals of a few days have resulted in complete cure *The evidence is however in conclusive* The treatment of persistent or frequently relapsing chronic cases is by splenectomy (my own experience of anti allergic treatment has been disappointing)

Very soon after removal of the spleen sometimes within minutes the platelet count rises sometimes to figures well above normal while the capillary resistance test becomes negative and both bleeding time and clot retraction become normal The platelets reach their *highest level at the end of about ten days and then gradually fall* sometimes to levels near the critical one

It is unusual for a relapse to occur even when the platelets fall to low levels and the bleeding time becomes prolonged In other words there is obviously some effect of splenectomy on capillary permeability *itself*

Recurrence of purpura after splenectomy occurs in about 20 per cent of cases but it is very rare for the recurrence to be as severe as the original disease If however recurrence is extremely severe the possibility of its being due to hypertrophy of an accessory spleen *overlooked at operation must be considered*

Many other methods of treatment have been suggested but none appears to be of any value X rays over the splenic area may lead to an increase of platelets but this is very rarely maintained



FIG 11 —The typical champagne bottle femora of Gaucher s disease Rarefaction of the wider part of the bottle is clearly shown

This condition is however not a manifestation of true rheumatism but appears to be anaphylactoid in origin

During the period of pains and swellings there is slight pyrexia *while slight purpura may occur at this time or later when the articular* manifestations have disappeared The purpuric haemorrhages occur into small urticarial wheals

Another anaphylactoid condition is *Henoch s purpura* in which the lesions are mainly in the intestine where the urticarial lesion occurs in the wall There is severe abdominal pain and the passage of blood per rectum In small children a diagnosis of intussusception may be made and indeed the affected area of the gut may become invaginated so that Henoch s purpura can be regarded as an occasional case of intussusception

If simple urticarial wheals with haemorrhage into them can be found on the skin the diagnosis is obvious and if there is a history of several similar attacks there can be little doubt

These two anaphylactoid manifestations are really closely allied and combinations of the two are quite common Thus there may be gastro intestinal disturbances accompanied by peri articular wheals As a general rule the prognosis in these conditions is good although relapses are common

An occasional complication is haematuria which seems to occur most frequently after several relapses

The only serious complication is *the development of nephritis* which is commoner than used to be supposed

Treatment

No specific treatment is available but anti histamine drugs may reduce the size of the articular exudations

In the rather uncommon cases in which the specific sensitizing agent can be discovered de sensitization can be tried but the results are not very good

Intramuscular injection of 20 mgm of citrin (vitamin P) twice a week seems to shorten the attack

SECTION V

SYMPTOMATIC BLOOD CHANGES

IN this section will be considered those changes that accompany various diseases both infective and non infective and in addition it will be necessary to include certain specific syndromes such as glandular fever and agranulocytosis which cannot easily be accommodated elsewhere

the splenomegaly and during the whole of this time relapse usually much less severe than the initial attack may occur

The anginose type in adults is very similar to the usual acute manifestations that occur in childhood but there is often membrane formation in the fauces

The febrile type is probably frequently overlooked because there is clinically nothing more than malaise or pyrexia Diagnosis in these cases depends entirely on blood examination

Blood

Characteristic blood changes occur in all cases but the time of onset varies considerably Thus there may be characteristic blood changes even before clinical symptoms occur but these are of course only found by chance In the fully developed case the essential features of the haemogram are an increased leucocyte count with a large proportion of glandular fever cells Even in those cases in which the leucocyte count is not raised the glandular fever cells may form 40–80 per cent of the total leucocytes The nature of these cells is still a little uncertain hence the non-committal name glandular fever cells It may be said that they resemble rather immature monocytes but it is possible that they are modified lymphocytes

When well developed such a blood picture is pathognomonic of glandular fever but similar perhaps identical cells may be found in smaller numbers in the blood in other diseases e g infective hepatitis It is therefore only when the percentage of these cells is high that a *definite diagnosis of glandular fever can be made by morphological* blood examination More significant is the Paul Bunnell test which depends upon the presence in the blood serum of these cases of an agglutinin for sheep s cells Unfortunately the titre of this agglutinin is sometimes extremely low in the early stages of the disease and then if the blood picture is also equivocal the diagnosis may be uncertain In most cases however the test becomes positive within a few days and remains so for several months although with a falling titre

The test is almost specific for glandular fever although in serum sickness a similar agglutinin can be found It can however be distinguished by adsorption tests

Complications

The great majority of cases of glandular fever run a benign course leading to complete recovery within weeks in children or months in adults Very rarely haemorrhagic manifestations have been described but these are not severe even haemorrhagic bephritis undergoes

CHAPTER XVIII

GLANDULAR FEVER

Infectious Mononucleosis

THIS malady which has the general characters of an acute infectious disease can occur in two main forms viz acute which is the common form in childhood and sub acute which is the usual type in adults

The acute type is of sudden onset usually with sore throat and enlargement of cervical glands which are much larger than would be expected from the condition of the fauces

Epistaxis sometimes quite severe may be the initial symptom even preceding the sore throat The temperature is high and other groups of glands become enlarged while the spleen may become palpable usually towards the end of the second week which is the time when the temperature often subsides

The whole course of the disease may extend to two or three weeks or a little more but occasionally lymphadenopathy and splenomegaly can still be detected after a year or two

In adults three classical types of glandular fever have been described but they overlap to some extent

In the glandular type which usually occurs between the ages of twenty and thirty the onset is sudden as in infancy with headache and fever up to about 103 Occasionally the headache is extremely severe and in some cases there is meningo encephalitis with many lymphocytes in the cerebro spinal fluid

After four to ten days a generalized morbilliform rash may appear This usually fades within a few days but fresh crops may occur for as long as another fortnight the temperature still being raised

During this period it is not uncommon to be able to detect other glandular enlargements which often do not manifest themselves until the eruption has disappeared Then the glands particularly the cervical ones become moderately enlarged and may be tender while other groups may be involved later About this time the spleen also becomes palpable while abdominal discomfort is usual and is probably due to enlargement of mesenteric glands

The lymphadenopathy may persist for a year or more as may also

the splenomegaly and during the whole of this time relapse usually much less severe than the initial attack may occur

The anginose type in adults is very similar to the usual acute mani festations that occur in childhood but there is often membrane formation in the fauces

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Blood

Characteristic blood changes occur in all cases but the time of onset varies considerably Thus there may be characteristic blood changes even before clinical symptoms occur but these are of course only found by chance In the fully developed case the essential features of the haemogram are an increased leucocyte count with a large proportion of glandular fever cells Even in those cases in which the leucocyte count is not raised the glandular fever cells may form 40–80 per cent of the total leucocytes The nature of these cells is still a little uncertain hence the non-committal name glandu lar fever cells It may be said that they resemble rather immature monocytes but it is possible that they are modified lymphocytes

When well developed such a blood picture is pathognomonic of glandular fever but similar perhaps identical cells may be found in smaller numbers in the blood in other diseases e g infective hepatitis It is therefore only when the percentage of these cells is high that a definite diagnosis of glandular fever can be made by morphological blood examination More significant is the Paul Bunnell test which depends upon the presence in the blood serum of these cases of an agglutinin for sheep s cells Unfortunately the titre of this agglutinin is sometimes extremely low in the early stages of the disease and then if the blood picture is also equivocal the diagnosis may be uncertain In most cases however the test becomes positive within a few days and remains so for several months although with a falling titre

The test is almost specific for glandular fever although in serum sickness a similar agglutinin can be found It can however be dis tinguished by adsorption tests

Complications

The great majority of cases of glandular fever run a benign course leading to complete recovery within weeks in children or months in adults Very rarely haemorrhagic manifestations have been des cribed but these are not severe even haemorrhagic bephritis undergoes

CHAPTER XVIII

GLANDULAR FEVER

Infectious Mononucleosis

THIS malady which has the general characters of an acute infectious disease can occur in two main forms viz acute which is the common form in childhood and sub acute which is the usual type in adults

The acute type is of sudden onset usually with sore throat and enlargement of cervical glands which are much larger than would be expected from the condition of the fauces

Epistaxis sometimes quite severe may be the initial symptom even preceding the sore throat The temperature is high and other groups of glands become enlarged while the spleen may become palpable usually towards the end of the second week which is the time when *the temperature often subsides*

The whole course of the disease may extend to two or three weeks *or a little more but occasionally* lymphadenopathy and *splenomegaly* can still be detected after a year or two

In adults three classical types of glandular fever have been described but they overlap to some extent

In the glandular type which usually occurs between the ages of twenty and thirty the onset is sudden as in infancy with headache and fever up to about 103 Occasionally the headache is extremely *severe and in some cases there is meningo-encephalitis with many* lymphocytes in the cerebro spinal fluid

After four to ten days a generalized morbilliform rash may appear This usually fades within a few days but fresh crops may occur for as long as another fortnight the temperature still being raised

During this period it is not uncommon to be able to detect other glandular enlargements which often do not manifest themselves until the eruption has disappeared Then the glands particularly the cervical ones become moderately enlarged and may be tender while *other groups may be involved later About this time the spleen also* becomes palpable while abdominal discomfort is usual and is probably due to enlargement of mesenteric glands

The lymphadenopathy may persist for a year or more as may also

and it is interesting to note that typical blood changes without any clinical signs may be found in other members of the family

Treatment

No specific treatment is available or necessary but attention to the throat will improve the patient s condition

complete resolution An occasional and very dangerous complication is spontaneous rupture of the spleen This only occurs if the organ is enlarged but the degree of splenomegaly need not be very great

Treatment

Penicillin or sulphonamides are probably useful in controlling the infection in the throat Convalescent serum in doses of 50 to 300 c c intramuscularly is said to shorten the course of the disease Recently chloromycetin has been advocated but it is still uncertain whether it has much effect

Acute Infectious Lymphocytosis

The clinical picture of this disease is very similar to that of glandular fever but is uncommon after the age of ten

Symptoms

After an incubation period of twelve–twenty one days signs of respiratory infection sometimes accompanied by sore throat develop At the same time abdominal pain commonly localized in the right iliac fossa may resemble appendicitis Severe headache is not uncommon and there may be stiffness of the neck and a positive Kernig sign

Morbilliform eruptions are also common

The disease lasts from a few days to a fortnight or so and complications are almost unknown

Glandular enlargement usually starting in the neck is not great but develops at some stage in every case while splenomegaly if present at all is only slight

Blood

A striking feature is leucocytosis usually in the region of 50 000 per c mm with more than 50 per cent of mature lymphocytes Anaemia and thrombocytopenia are unusual

The haemogram thus resembles that of lymphatic leukaemia but the course of the disease is totally different A similar blood picture may also be seen in some cases of whooping cough

The Paul Bunnell reaction is always negative and this is a most essential step in differential diagnosis from glandular fever

Aetiology

There seems no doubt that the disease is due to a virus although this has not been isolated This degree of infectivity is relatively high

neutrophils The total white cell count is below 2 500 per c mm and may even be below 50 per c mm Obviously in these more severe cases the whole of the leucopoietic apparatus is affected

In agranulocytosis in the strict sense of the term there is no anaemia or thrombocytopenia but in primary splenic neutropenia these two factors may be super added

Aetiology

If the term agranulocytosis be confined to that condition in which there is reduction of neutrophils it may be said that there is no such condition as primary agranulocytosis It is always due to some noxious agent often a sedative drug

There seems little doubt that the most important of all agents that may cause agranulocytosis is amidopyrine (pyramidon) Indeed it may be said that this drug should never be used but if it is felt that it should be employed because of its pain alleviating value it should always be prescribed by name This point is stressed because there are on the market a number of compounds in which amidopyrine is employed and the patients may well be exposed to great danger without the physician being clearly aware of what is happening

Not all people are equally sensitive to amidopyrine and many people can take it with impunity but sensitization may occur at any time and once it has occurred a very small dose may precipitate acute and fatal agranulocytosis

Other drugs such as the sulphonamides arsenicals tridione the anti histamines thiouracil etc may also cause agranulocytosis although very rarely

Agranulocytosis may also occur in cases of overwhelming infection

The mechanism by which the neutropenia is brought about is probably not always the same In the less severe cases there is a defect in the maturation of the precursors of the granulocytes in the bone marrow but in the fulminating cases there is destruction of these precursors Obviously it is in the latter type that the prognosis is the worst and for this reason marrow puncture is extremely useful in assessing the probable outcome of the disease

Treatment

Obviously the first step is the withdrawal of any drug that might be the cause of the disease while the second step is the treatment of the infection This is essential in order to diminish the strain on the bone marrow For this reason penicillin is essential and fortunately

AGRANULOCYTOSIS

THIS is a disease in which as a result of great diminution or disappearance of granular leucocytes severe infection usually of the throat develops

Symptoms

There is rapid onset of severe almost necrotic infection of the fauces with pyrexia and extreme exhaustion This condition is commonest in elderly women and is usually rapidly fatal

Other mucosae e g of the vagina or rectum may be the site of the presenting signs but wherever the lesions they are rapidly progressive and lead to widespread destruction

Several clinical types have been described

1 Fulminating as above acute and rapidly fatal
2 Sub-acute in which the infection is less severe and recovery may occur within a few weeks
3 Recurrent in which the individual attacks are of the sub acute type
4 Chronic There is no distinctive clinical picture of chronic hypogranulocytosis but these patients complain of frequent minor infective conditions such as sore throats accompanied by an excessive degree of malaise The nature of the condition is only detectable by blood examination It is however important because this chronic state may at any time become acute
5 Cyclical In this rare condition mild faucial lesions occur at intervals each being preceded and accompanied by great reduction of neutrophil leucocytes
6 Primary splenic neutropenia This is probably a very different condition being in fact a manifestation of hypersplenism This is the only form of agranulocytosis in which the spleen is palpable and which is cured by splenectomy

Blood

The essential feature of the blood picture is great reduction in the number of leucocytes mainly due to diminution or absence of

CHAPTER XX

SYMPTOMATIC BLOOD CHANGES

IN this chapter the blood changes that occur in association with various diseases infective and otherwise will be described Many blood examinations are undertaken in diseases which are obviously not essentially disorders of the haemopoietic system and the results are often of great diagnostic value

Infection

In the majority of infections changes in the number and distribution of the various types of leucocytes are found and although there are practically no pathognomonic haemograms in these diseases much diagnostic and prognostic information can be obtained if the principles of interpretation are appreciated

Broadly it may be said that acute infections by cocci of all types are accompanied by an increase in the number of neutrophils while the bacillary infections are usually associated with lymphocytosis whether absolute or relative

Coccal Infections

The height of the leucocytosis which occurs in most of these infections is not indicative of the intensity of the infection It is therefore not sufficient to note the number of leucocytes per c mm the differential count is far more important

In all these infections there is evidence of difficulty on part of the marrow in meeting the increased demands For this reason slightly immature neutrophils appear in the peripheral blood These may be staff forms or in more severe cases juvenile metamyelocytes or even myelocytes Obviously then some idea of the efficiency and intensity of marrow response can be obtained by enumerating percentages of each of these types of neutrophil viz myelocyte juvenile staff and polymorph This is known as the Schilling index but far more delicate indication is the so-called Arneth count which is however too complicated for ordinary use Essentially it depends upon the view that the more mature the neutrophil the more

the organisms are almost invariably penicillin sensitive Occasion ally streptomycin has been used in conjunction with penicillin

Obviously attention to local infections is also important

It would seem reasonable to attempt to supply the various substances required for maturation of leucocytes in order to give the best possible chance to any parent cells that are still viable For this reason pentose nucleotide has been widely used At least 50 c c in twenty four hours should be given in divided doses by intramuscular injection and this must be continued until the granulocyte count starts to rise about the fourth or fifth day Obviously pentose nucleo tide cannot be expected to have any effect in aplastic conditions of the marrow and indeed it is still uncertain whether it is of any therapeutic value

Intravenous injection of vitamin B6 (pyridoxine) in doses of about 200 mgms daily giving a 10 per cent solution in saline does appear to be of value particularly in agranulocytosis due to thiouracil In deed pyridoxine given by mouth is stated to be a useful prophylactic against the development of agranulocytosis during treatment of thyrotoxicosis with this drug

The value of blood transfusion is doubtful Anaemia is not part of the picture of true agranulocytosis and in some cases the infusion of blood is followed by a fall in the number of white cells

The prevention of agranulocytosis is obviously of far greater im portance than is the treatment of an established case If however it is necessary for a patient to be treated with a drug that is liable to cause agranulocytosis frequent leucocyte counts both total and differential should be carried out Even this is not however, a com plete safeguard because sudden development of agranulocytosis even when the leucocyte count has previously been normal is by no means uncommon In general therefore drugs that are liable to cause this disease should be avoided

infections with haemolytic organisms the anaemia is not mainly due to blood destruction but results from defective formation in the marrow It has already been mentioned that iron appears to be fixed in inflammatory areas and so ceases to be available for erythropoiesis it is this fact that explains the anaemia of many infections In addition however there are other nutritional deficiencies which prevent the erythropoietic cells from undergoing normal development In other words the anaemia of most infections depends upon a defect of maturation which is due to absence of substances needed for erythropoiesis

Abortus Fever

In the absence of treatment these infections with brucella are very prolonged and will give rise to only a moderate degree of anaemia *which is usually hypochromic and strikingly microcytic* There are no constant changes in the leucocytes and oddly enough the sedimentation rate is often normal The absence of striking blood changes is surprising because marrow puncture often reveals the presence of the typical granulomatous foci

Actinomycosis

In the early stages of the infection there is high leucocytosis up to 30 000 per c mm the great majority of the cells being neutrophils with a well marked shift to the left The height of the leucocyte count is greatest in the cases with the widest extension of the infection Anaemia is not an invariable part of the picture but in severe abdominal infections it becomes intense while a shift to the left of the neutrophils is extreme sometimes even with a high percentage of myelocytes

Appendicitis

Probably more leucocyte counts are asked for in cases of suspected intra abdominal inflammation than in any other type of disease but unfortunately the principles of interpreting the results are still not as well known as they should be

In the early stages it is uncommon to find a leucocyte count of less than 10 000 per c mm with 75–85 per cent of neutrophils but lower figures than these accompanied by a shift to the left of the Schilling count should be regarded as being at least as cogent an evidence as is a high total leucocyte count

Further rise of the total number of leucocytes and greater shift to the left occurs when suppuration develops but here again it is the shift to the left rather than the total figure that is important

complicated is its nuclear lobulation but for ordinary purposes the Schilling index suffices

In addition to what may be called gross qualitative changes in the neutrophils more delicate ones should also be studied e g clumping of the cytoplasmic granules vacuolation of the cytoplasm and pyknosis of the nucleus all these are indicative of severe infection

It is well known that in overwhelming infections the cellular defences of the body may be overcome and in such cases there is no leucocytosis and indeed there may be leucopenia but in spite of this there is immaturity of the neutrophil picture (shift to the left) and the presence of many more or less immature cells

It must be realized that the leucocyte picture is not a static one In every infection there is a series of changes from the earliest stage until death or recovery occurs In general it may be said that neutro phil leucocytosis accompanies the acute stage of coccal infections while at the same time the number of eosinophils greatly diminishes then when recovery commences the number of neutrophils both absolute and relative decreases while the lymphocytes rise to num bers greater than normal (post infective lymphocytosis) In some cases an eosinophilia accompanies this lymphocytosis while in others it succeeds it This series of changes occurs in all such infections but is particularly striking during and after a pneumonic infection

Bacillary Infections

As a general rule there is reduction in the number of neutrophils with however some shift to the left of the Schilling index while at the same time there is either relative or absolute lymphocytosis Typhoid fever is an excellent example of leucopenia with a relative lymphocytosis (p 199) whereas whooping cough is an example of absolute lymphocytosis evoked by a bacillary infection

Lymphocytosis is however not to be regarded as pathognomonic of bacillary infections because it is also found as mentioned above *after* any acute infection while it is also characteristic of most chronic infections whatever their cause Equally the absence of lymphocy tosis cannot be regarded as conclusive evidence that an infection is not due to bacilli because when such conditions as empyema of the gall bladder follow an infection by B coli neutrophil leucocytosis develops

Anaemia in Infections

Anaemia of varying degree develops during the course of all infections except the most transient ones Even in the case of

a beneficial effect on the arthritis but as a rule this is not permanent.

Chicken Pox

There is no pathognomonic leucocyte picture but in the incubation stage there is slight neutrophilia which is followed by moderate lymphocytosis A few plasma cells can be found and during con valescence post infective eosinophilia up to 10 or 15 per cent is common

As in all virus diseases the blood picture may occasionally be of leukaemoid type with metamyelocytes and myelocytes and occasion ally a few normoblasts Striking though this picture is it does not appear to have any special prognostic significance

Cholera

The blood is dark as a result of dehydration but at least in severe cases there is true leucocytosis i e an increase of white cells greater than can be accounted for by haemo-concentration The same is true of the platelets which may attain very high figures When the infection subsides hypochromic anaemia becomes manifest

Dengue

This is a virus infection in which there is rapid onset of leucopenia counts as low as 1 000 per c mm being common by the end of the first week All types of white cells are reduced in number but the lymphocytes are less so than the neutrophils

Dysentery

In bacillary dysentery moderate neutrophilia is usual while in chronic cases a severe anaemia may develop This is usually hypochromic and microcytic but occasionally macrocytosis is well marked.

In amoebic dysentery anaemia is more striking than any of the leucocyte changes and the same is true of ulcerative colitis In both these diseases there may be hypoprothrombinaemia sometimes sufficiently severe to result in haemorrhage

Diphtheria

In moderately severe cases there is leucocytosis up to 30 000 per c mm while in very severe cases there is leucopenia with extreme shift to the left Anaemia is relatively uncommon but may occur during convalescence in severe cases

Decrease in the leucocyte count may indicate subsidence of the inflammation but it may also indicate overwhelming infection and imminent collapse In *the former the leftward shift will be found* to be decreasing whereas in the latter it will be increasing

In children interpretation of the blood changes is often more difficult because up to the age of eight or ten there may be lymphocytosis instead of the typical neutrophilia but even so there will be shift to the left of the neutrophils

Unfortunately leucocyte counts in cases of suspected appendicitis can as a rule do no more than indicate the existence of an acute infection but in the differentiation of acute inflammations in the abdomen from mesenteric thrombosis there are significant points Thus in the early stages of mesenteric thrombosis before peritonitis supervenes there is always leucopenia which is due to reduction of all type of white blood cells

Arthritis

In suppurative arthritis the blood changes are those of any acute infection

In rheumatoid arthritis a moderate degree of hypochromic anaemia is common but in severe and very prolonged cases the anaemia may reach serious levels It appears to be due to iron deficiency but is rarely improved and never cured by oral administration of iron whereas intravenous injections rapidly although only temporarily relieve it It appears therefore that there is some defect of absorption from the intestine

The leucocyte count shows no striking variations but moderate leucopenia with relative lymphocytosis is usual

There is no correlation between the sedimentation rate and the chronicity of the condition

In Still s disease in children there are many of the clinical features of rheumatoid arthritis but in addition there are generalized lymphadenopathy and splenomegaly while in a similar malady that occurs in adults Felty s syndrome there is rheumatoid arthritis with splenomegaly but little or no lymphadenopathy In both these conditions anaemia of varying degree is common together with loss of weight and progressive weakness sometimes accompanied by brownish pigmentation of the exposed skin

A striking blood change is leucopenia which may be severe e g 800 per c mm This depends mainly sometimes entirely on reduction of granular leucocytes and is due to hypersplenism Removal of the spleen relieves the leucopenia and in some cases exerts

chromic anaemia follows severe influenzal infection Influenzal pneumonia or any other intercurrent infection is accompanied by neutrophilia

Liver

The hyperchromic megalocytic anaemia that may accompany advanced cirrhosis has already been mentioned (p 80) In *infective hepatitis* there is leucopenia during the early stages of the disease even before jaundice develops Usually this is due to neutropenia but sometimes all types of white cells are reduced in number A small percentage of white cells with the characters of glandular fever cells can almost always be found while it is unusual to find less than 2 or 3 per cent of plasma cells in the peripheral blood Such a blood picture is of value in differentiating between infective hepatitis and Weil s disease in which high neutrophilia occurs with extreme left ward shift metamyelocytes and myelocytes often being numerous Anaemia may become severe and thrombocytopenia may lead to haemorrhages while hypothrombinaemia is common and of course aggravates the haemorrhagic tendency

In the condition commonly known as *Banti s disease* cirrhosis of the liver occurs in the later stages and it is probably best to include this syndrome under the heading of hepato-lineal fibrosis or conges tive splenomegaly

The disease runs a very prolonged course Thus for a number of years there is nothing more than slowly progressive splenomegaly with gradually increasing hypochromic anaemia Then the liver becomes enlarged and jaundice of obstructive type develops This second stage lasts a year or two and then there develops the final stage of advanced cirrhosis of the liver ascites haemorrhages especially from varicosifies at the lower end of the oesophagus cachexia and death The disease commences in early adult life and it is unusual to lead to death before the age of thirty five or forty

For some years after the onset the red corpuscles do not fall below 3 million but the colour index is a good deal less than 1 0 At this stage the condition may obviously be mistaken for chronic hy pochromic anaemia Moderate leucopenia is usual but the platelets do not fall until the advanced stage

The pathogenesis of the disease is still not quite certain but it is now commonly attributed to portal hypertension For this reason the older method of treatment by splenectomy has been superseded by the more heroic one of performing a porto-caval shunt There is however little evidence that the more dangerous operation is better

Endocarditis

In sub-acute bacterial endocarditis the blood changes are variable but may be of considerable diagnostic importance especially in those cases in which the blood culture is persistently negative Anaemia occurs early and is progressive but leucocytosis is often absent at any rate until embolic phenomena are striking It is however uncommon to see cases of this disease without monocytosis These cells resemble histiocytes rather than the typical monocytes of the blood and some of them show signs of phagocytic activity The percentage of monocytes may be as high as forty and their numbers can be increased by vigorous rubbing of the skin before the films are made It seems certain that monocytes are sequestrated in capillaries If this is the case it would explain many of the haemorrhagic features of sub acute bacterial endocarditis which has been regarded by some writers as being a toxic endotheliosis

In ulcerative endocarditis the ordinary changes of acute coccal infections are to be expected

Erysipelas

The series of leucocyte changes is that typical of coccal infections but erysipelas like pneumonia is usually followed by well marked post infective lymphocytosia and eosinophilia Indeed the former may transiently be so high as to occasion suspicion of chronic lymphatic leukaemia

German Measles

In rubella there is a striking blood change viz the presence of plasma cells in considerable numbers in the peripheral blood In addition there is a considerable number of other cells in which the nucleus is not excentric but the cytoplasm is as intensely basophil as that of the plasma cells (Turk cells) In many cases these two types of elements together form 10 to 20 per cent of the total white cells There is no other infective condition in which such a degree of haemic plasma cytosis occurs and its presence is a useful point in differential diagnosis from for example scarlet fever

Influenza

In the absence of secondary infection leucopenia is invariable but only in severe cases do the white cells fall as low as 1 000 per c mm with very intense relative lymphocytosis which may be sufficient to arose a suspicion of aleukaemic lymphatic leukaemia

In cyanosed patients there is erythrocytosis Moderate hypo-

those accompanied by endocarditis the red corpuscles may fall as low as 2 million

Neutrophil leucocytosis is the rule and all complications are accompanied by an increased leucocyte count This is however not as certain a guide to the severity and progress of the disease as is the sedimentation rate

Scarlatina

In cases of ordinary severity leucocytosis up to 40 000 per c mm is the rule 80 to 90 per cent of the cells being neutrophils which show a great shift to the left myelocytes being numerous in some cases The leucocytosis disappears or subsides by the end of the second week *but in fulminating cases leucocytosis is absent although the* shift to the left is well marked

At the onset of the disease the eosinophils fall but in some cases in which the cutaneous eruption is widespread but the disease is not very severe eosinophilia develops whereas in rather more severe but not fulminating cases eosinophils only begin to rise towards the end of the first week then they fall but rise again when the infection has completely subsided

Thrombocytosis up to 500 000 per c mm may be found at the height of the disease but in fulminating and haemorrhagic cases thrombocytopenia and haemorrhages are characteristic

Smallpox

At the height of the disease the white cell count falls to normal or rather lower mainly as a result of decrease of neutrophils but when pustulation occurs the leucocyte count rises to 30 000 per c mm or higher The shift to the left is very great at the beginning of the vesicular stage as many as 15 per cent of myelocytes being found

Post infective lymphocytosis and eosinophilia are very well marked in smallpox and in the absence of an adequate history such a post infective blood picture may lead to confusion

Tuberculosis

Acute Miliary Tuberculosis

As a rule there is intense leucopenia the white cell count being in the region of 1 000 per c mm It may be said that the less the reduction of the leucocytes the more sub-acute or chronic is the process

Acute Pulmonary Tuberculosis

In tubercuous broncho-pneumonia there is usually leucopenia but occasionally slight neutrophilia occurs This is however never

What is certain is that if either operation is to arrest the course of the disease it must be performed in the relatively early stages certainly before cirrhosis is clinically appreciable

Measles

The blood picture is similar to that of German measles but the percentage of plasma cells is little above two or three Although the *acute stage of the disease is accompanied by relative lymphocytosis* post infective lymphocytosis is also very striking

Meningitis

When due to pyogenic cocci there is high neutrophilia except in cases of overwhelming infection In more chronic cases hypochromic anaemia invariably develops

Pyococcal meningitis is one of the conditions in which a leukaemoid blood picture may occur

Mumps

There is leucopenia in the early stages the count rarely being above 3 000 per c mm but often with slight absolute lymphocytosis and monocytosis If orchitis develops neutrophilia supervenes

Pneumonia

In both lobar and broncho pneumonia neutrophilia is the rule and the ordinary criteria apply

In virus pneumonia the number of leucocytes is normal or moderately reduced sometimes with relative or absolute lymphocytosis In some cases cold agglutinins are present in the serum and occasionally lead to the development of an acute haemolytic anaemia The absence of cold agglutinins is however not to be regarded as excluding the diagnosis of virus pneumonia because *this is undoubtedly* not an aetiological entity but can be caused by various perhaps closely allied viruses

Poliomyelitis

In the pre paralytic stage there is moderate neutrophilia but this disappears with the onset of the paralysis and as a rule both the red and white count then become normal and remain so

Rheumatic Fever

Acute rheumatism is associated with hypochromic anaemia except in the very slightest attacks In the more severe cases especially

after a week or two the eosinophils rise to at least 25 per cent and in some cases as high as 80 per cent

Whooping Cough

In the early stages there are no striking blood changes but when the paroxysmal phase commences leucocytosis is the rule This increase of white cells is due to lymphocytosis and the total count may be as high as 100 000 with 80 to 90 per cent of lymphocytes the picture closely resembling that of lymphatic leukaemia especially because a few lymphoblasts may also be present

The bone marrow is however not infiltrated by lymphocytes

The highest figures are seen in the youngest age group older children show only a moderate leucocytosis and usually a slighter degree of lymphocytosis

Usually the blood picture becomes normal often before the end of the paroxysmal stage

sufficiently high to lead to confusion with coccal pneumonia Fur thermore hypochromic anaemia develops rapidly and becomes far more intense than in coccal pneumonia

Chronic Pulmonary Tuberculosis

In spite of the enormous amount of work on the blood changes in this disease there is still no agreement as to the significance of the various changes in the haemogram It may therefore, be said that in all cases the sedimentation rate is a useful indication of the intensity of the tuberculosis process Further that raised total leucocyte count with the neutrophils above 65 per cent indicates active progress of the disease and this is especially true if the monocyte count is also raised A total count within approximately normal limits not accompanied by monocytosis usually indicates quiescence and if the lymphocytes are above 35 per cent it is commonly held that healing has commenced

The platelet count has been regarded as being of prognostic significance because these elements are increased in the active phase of the disease and return to normal or sub normal during the healing process The errors inherent in every method of enumerating blood platelets diminishes the value of this test

Acute miliary tuberculosis is one of the conditions in which leukaemoid blood pictures are particularly common counts as high as 400 000 per c mm occasionally being recorded but similar pictures may occur in any case of tuberculosis at any stage It is only by marrow puncture that leukaemia can be excluded

Glandular Tuberculosis

The interpretation of the haemogram differs somewhat from that in pulmonary tuberculosis because there is always an increase of monocytes in the glandular cases and this has not the same bad significance that it has in pulmonary tuberculosis

Typhoid Fever

The characteristic feature is leucopenia with relative lymphocy tosis This develops quite early even before there are any unequivocal clinical signs of the disease Leucocytosis occurs in the presence of such complications as perforation

Trichiniasis

This helminth infestation is especially interesting because there is never a leucocytosis which is not accompanied by eosinophilia but

after a week or two the eosinophils rise to at least 25 per cent and in some cases as high as 80 per cent

Whooping Cough

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EPILOGUE

IT is customary to lament the increase of specialism in medicine and this process is at least as striking in haematology as in any other branch It is for this reason that books on haematology have become larger and larger and more and more incomprehensible to the practitioner of medicine It is noteworthy that other disciplines which were once the preserve of the physician and surgeon have undergone a comparable evolution It is not so long ago that the authors of books on for instance chemistry were always M D but to-day that would be remarkable Still more recently it was usual for authors of text books of pathology to be practising physicians The establishment of pathology as a separate subject with its own teachers and research workers is a modern innovation The late Professor A E Boycott was one of those who insisted most strongly that pathology is a scientific discipline in its own right quite apart from its pragmatic value in the art of medicine It is no longer possible for the practising physician to be conversant with all the ramifications of subjects ancillary to his own and this is equally true in haematology which is no longer simply that branch of medicine which deals with disorders of the blood and haemopoietic organs

The discovery of the blood groups and of their importance in con nexion with transfusion was a matter of immediate importance to the practitioner but the complicated researches on their inheritance has given rise to an enormous anthropological and genetic literature of its own which is so complicated that it cannot possibly be con sidered as forming part of the necessary equipment of the doctor Developing *pari passu* there has been the rise of another specialized subject that of immuno-haematology which again is so abstruse as to lie outside the normal cognizance of the practitioner

These two examples will suffice to show that there is a science of pure haematology the results of which are not necessarily part of the corpus of practical medicine probable though it is that much of the information will become of value later If the writers of books intended for the physician would bear such facts in mind books on clinical haematology will become smaller and of more use to the practitioner

All this is not to suggest that the doctor may not be interested in the fundamentals and the lines of scientific advance but such an interest must be to a great extent academic.

Admittedly acceptance of this view would mean that there would be at least three types of books viz the highly technical intended for the academic worker whose job is the opening up of new knowledge the students which would have to contain a sufficient amount of basic knowledge to permit of understanding and the third type which is the practitioners handbook In the last named there would be a distillate of the knowledge that has been acquired first at the bedside and secondly in the various types of laboratories in which haematology (and indeed cytology as a whole) is pursued Such a book should contain a sufficient amount of basic information on why but its aim should be the more practical one of how to use the knowledge in diagnosis and treatment

As the present book is as far as I know the first attempt to produce a practitioners handbook of blood diseases it seems necessary to give some indication of the activities of the academic haematologist and of his aims although much of the information is second hand garnered from reading and from the ample knowledge of those friends who can pursue their researches free from the turmoil of practice

One of the most exciting chapters in modern cytology (and therefore in morphological haematology) is that of histo-chemistry

Obviously the whole process of staining blood films is an essentially chemical one and it has long been known that nuclei are basophilic while cytoplasm is at least in mature cells, acidophilic Why is this? And why is the outstanding sign of maturation of the cytoplasm the transformation from basophilia into acidophilia?

Among the first steps in solving the problem was the discovery that ribonucleic acid and desoxy ribose nucleic acid could be stained differentially so that the whole series of chemical metamorphoses during maturation could be followed in detail Then came the discovery of the enzyme ribonuclease which will dissolve out ribonucleic acid thus making it possible to determine the exact position of this substance in cells There seemed hope that we were approaching that fundamental aetiological question Why do cells divide? We still do not know the answer but it is clear that along these lines the explanation will be found

Next calling in the aid of the physicist the haematologist attempted with considerable success to trace these changes quantitatively by the aid of photometric analysis and soon it should be

possible to express degrees of basophilia in definite units rather than in terms of 'more or less

Further insight into cellular structure is being obtained by the phase contrast and electron microscopes so that mitochondria and the ultra structure of cytoplasm are almost as well known to the researcher as are nuclei to the clinician

The immuno-haematologist in his search for sub-groups and atypical antibodies is continually adding more to our knowledge of the haemolytic anaemias

Any one and every one of these modern procedures may give birth to knowledge applicable in medical practice and those who enjoy keeping up-to-date may find the appended li t admittedly very in complete useful as a guide to their reading One warning is how ever necessary it is that the language of the sub-disciplines of haematology each one of which is becoming more and more inde pendent is often complicated and much of it is more likely to be more readily understood by the geneticist the bio-chemist and the micro physicist than by those whose job is primarily the diagnosis and treatment of disease For the last named a number of books dealing mainly or entirely with the medical aspects of haematology has also been appended

Researches of a more immediately practical character are those that have been carried out with radio-active iron and these have en abled the mode of absorption storage and utilization of this essential haemopoietic substance to be followed

Also of practical significance are the laboratory researches on mitotic poisons and cytostatic substances in general From these labours have resulted such substances as urethane and nitrogen mustard Those who regard the leukaemias as being neoplastic diseases will continue to hope that such researches will result in a cure of malignant tumours in general

Amazing though it is the problem of blood coagulation is still un solved or perhaps more accurately still has innumerable solutions each one of which is regarded as being satisfactory by its discoverer The literature that has grown up around this subject is enormous but, in spite of the gaps in our knowledge results of practical importance especially in connexion with the use of anti-coagulants in throm botic disorders has become of great value

In order that those who may wish to follow the most recent advances in the field of haematology can do so a list of the journals devoted to the subject is appended

Blood (American)

Acta Haematologica (The Journal of the European Society of Haematology)
Revue d Hématologie (French)
Le Sang (French)
Haematologica (Italian)
Folia Haematologica (German)

Each issue of these journals contains papers on all aspects of haematology but relatively few are of immediate interest to the practising physician

Reference books are numerous but all suffer from the disadvantage that they are not quite up to date The following are among the most useful

Clinical Hematology W W Wintrobe (2nd edition 1946)
Blood and Blood Diseases Heilmeyer & Begemann (1951)
(This unique volume is in German but is certainly the most complete reference book on Haematology available)
Disorders of the Blood L E H Whitby and C J C Britton (6th edition 1950)

Those interested in the still almost entirely academic subject of the ultra structure of cells will find details in
Cytologie Sanguine M Bessis (French) (1948)

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